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(54) Title: A METHOD FOR GENERATING BIRNAVIRUS FROM SYNTHETIC RNA TRANSCRIPTS

(57) Abstract

A system for the generation of live Birnavirus such as infectious bursal disease virus (IBDV), a segmented double-stranded (ds)RNA virus of the *Birnavirdae* family, using synthetic transcripts derived from cloned DNA has been developed. Independent full-length cDNA clones were constructed which contained the entire coding and non-coding regions of RNA segments A and B of IBDV, respectively. Synthetic RNAs of both segments were produced by *in vitro* transcription of linearized plasmids with T7 RNA polymerase. Transfection of Vero cells with combined plus-sense transcripts of both segments generated infectious virus as early as 36 hours post-transfection. The development of a reverse genetics system for dsRNA viruses will greatly facilitate studies of the regulation of viral gene expression pathogenesis, and design of a new generation of live and inactivated vaccines.

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A METHOD FOR GENERATING BIRNAVIRUS FROM SYNTHETIC RNA TRANSCRIPTS

Background of the Invention

Infectious bursal disease virus (IBDV), a member of the *Birnaviridae* family, is the causative agent of a highly immunosuppressive disease in young chickens (Kibenge, F.S.B., et al., *J. Gen. Virol.*, 69, 1757-1775 (1988)). Infectious bursal disease (IBD) or Gumboro disease is characterized by the destruction of lymphoid follicles in the bursa of Fabricius. In a fully susceptible chicken flock of 3-6 weeks of age the clinical disease causes severe immunosuppression, and is responsible for losses due to impaired growth, decreased feed efficiency, and death. Susceptible chickens less than 3 weeks old do not exhibit outward clinical signs of the disease but have a marked infection characterized by gross lesions of the bursa.

The virus associated with the symptoms of the disease is called infectious bursal disease virus (IBDV). IBDV is a pathogen of major economic importance to the nation and world's poultry industries. It causes severe immunodeficiency in young chickens by destruction of precursors of antibody-production B cells in the bursa of Fabricius. Immunosuppression causes increased susceptibility to other diseases, and interferes with effective vaccination against Newcastle disease, Marek's disease and infectious bronchitis disease viruses.

There are two known serotypes of IBDV. Serotype I viruses are pathogenic to chickens whereas serotype II viruses infect chickens and turkeys. The infection of turkeys is presently of unknown clinical significance.

IBDV belongs to a group of viruses called *Birnaviridae* which includes other bisegmented RNA viruses such as infectious pancreatic necrosis virus (fish), tellina virus and oyster virus (bivalve mollusks) and drosophila X virus (fruit fly). These viruses all contain high molecular weight (MW) double-stranded RNA genomes.

The capsid of the IBDV virion consists of several structural proteins. As many as nine structural proteins have been reported but there is evidence that some of these may have a precursor-product relationship (Kibenge,

F.S.B., et al., *J. Gen. Virol.*, 69, 1757-1775 (1988)). The designation and molecular weights of the viral proteins (VP) are as shown below.

Viral Protein	Molecular Weight
VP1	90 kDa
VP2	41 kDa
VP3	32 kDa
VP4	28 kDa
VP5	17 kDa

Two segments of double-stranded RNA were identified in the genome of IBDV. The IBDV genome consists of two segments of double-stranded (ds)RNA that vary between 2827 (segment B) to 3261 (segment A) nucleotide base pairs (Mundt, E. et al., *Virology*, 209, 10-18 (1995)). The larger segment A encodes a polyprotein which is cleaved by autoproteolysis to form mature viral proteins VP2, VP3 and VP4 (Hudson, P.J. et al., *Nucleic Acids Res.*, 14, 5001-5012 (1986)). VP2 and VP3 are the major structural proteins of the virion. VP2 is the major host-protective immunogen of IBDV, and contains the antigenic regions responsible for the induction of neutralizing antibodies (Azad, et al., *Virology*, 161, 145-152 (1987)). A second open reading frame (ORF), preceding and partially overlapping the polyprotein gene, encodes a protein (VP5) of unknown function that is present in IBDV-infected cells (Mundt, E., et al., *J. Gen. Virol.*, 76, 437-443, (1995)). The smaller segment B encodes VP1, a 90-kDa multifunctional protein with polymerase and capping enzyme activities (Spies, U., et al., *Virus Res.*, 8, 127-140 (1987); Spies, U., et al., *J. Gen. Virol.*, 71, 977-981 (1990)).

It has been demonstrated that the VP2 protein is the major host protective immunogen of IBDV, and that it contains the antigenic region responsible for the induction of neutralizing antibodies. The region containing the neutralization site has been shown to be highly conformation-dependent. The VP3 protein has been considered to be a group-specific antigen because

it is recognized by monoclonal antibodies directed against it from strains of both serotype I and II viruses. The VP4 protein appears to be a virus-coded protease that is involved in the processing of a precursor polyprotein of the VP2, VP3 and VP4 proteins.

Although the nucleotide sequences for genome segments A and B of various IBDV strains have been published, it was only recently that the complete 5'- and 3'-noncoding sequences of both segments were determined. The 5'-noncoding region of IBDV segments A and B contain a consensus sequence of 32 nucleotides, whereas the 3'-noncoding terminal sequences of both segments are unrelated, but conserved among IBDV strains of the same serotype (Mundt, E. et al., *Virology*, 209, 10-18 (1995)). These terminii might contain sequences important in packaging and in the regulation of IBDV gene expression, as demonstrated for other dsRNA containing viruses such as mammalian and plant reoviruses, and rotaviruses (Anzola, et al., *Proc. Natl. Acad. Sci. USA*, 84, 8301-8305 (1987); Zou, S., et al., *Virology*, 186, 377-388 (1992); Gorziglia, M.I., et al., *Proc. Natl. Acad. Sci. USA*, 89, 5784-5788 (1992)).

In recent years, a number of infectious animal RNA viruses have been generated from cloned cDNA using transcripts produced by DNA-dependent RNA polymerase (Boyer, J.C., et al., *Virology*, 198, 415-426 (1994)). For example poliovirus, a plus-stranded RNA virus; influenza virus, a segmented negative-stranded RNA virus; rabies virus, a non-segmented negative-stranded RNA virus; all were recovered from cloned cDNAs of their respective genomes (van der Werf, S., et al., *Proc. Natl. Acad. Sci. USA*, 83, 2330-2334 (1986); Enami, M., et al., *Proc. Natl. Acad. Sci. USA*, 87, 3802-3805 (1990); Schnell, M.J., et al., *EMBO J.*, 13, 4195-4205 (1994)). For reovirus, it was shown that transfection of cells with a combination of SSRNA, dsRNA and *in vitro* translated reovirus products generated infectious reovirus when complemented with a helper virus from a different serotype (Roner, M.R., et al., *Virology*, 179, 845-852 (1990)). However, to date, there has been no report of a recovered infectious virus of segmented dsRNA genome from synthetic RNAs only.

Summary of the Invention

This invention relates to the infectious bursal disease virus (IBDV) that is associated with Gumboro disease of young chickens. More particularly, this invention relates to a system for the generation of infectious bursal disease virus (IBDV) using synthetic transcripts derived from cloned cDNA. The present invention will facilitate studies of the regulation of viral gene expression, pathogenesis and design of a new generation of live and inactivated vaccines.

Detailed Description of the Invention

In an effort to develop a reverse genetics system for IBDV, three independent full-length cDNA clones which contain segment A of serotype I strain D78 or serotype II strain 23/82 and segment B of the serotype I strain P2, respectively, were constructed. Synthetic RNAs of segments A and B were produced by *in vitro* transcription reaction on linearized plasmids with T7 RNA polymerase. Transcripts of these segments, either untreated or treated with DNase or RNase, were evaluated for the generation of infectious virus by transfection of Vero cells.

The present inventors have demonstrated that synthetic transcripts derived from cloned DNA corresponding to the entire genome of a segmented dsRNA animal virus can give rise to a replicating virus. The recovery of infectious virus after transfecting cells with synthetic plus-sense RNAs derived from cloned cDNA of a virus with a dsRNA genome (IBDV) completes the quest of generating reverse infectious systems for RNA viruses. A number of investigators have generated infectious animal RNA viruses from cloned cDNA (Boyer, J.C., et al., *Virology*, 198, 415-426 (1994)). Van der Werf et al. were first to generate poliovirus, a plus-stranded RNA virus, using synthetic RNA produced by T7 RNA polymerase on cloned cDNA template (van der Werf, S., et al., *Proc. Natl. Acad. Sci. USA*, 83, 2330-2334 (1986)). later, Enami et al. rescued influenza virus, a segmented negative-stranded RNA virus (Enami, M., et al., *Proc. Natl. Acad. Sci. USA*, 87, 3802-3805 (1990)); and Schnell et al. generated rabies virus, a non-segmented negative-stranded RNA virus, from cloned cDNAs of their respective genomes (Schnell, M.J., et

al., *EMBO J.*, 13, 4195-4205 (1994)). Roner et al. developed an infectious system for a segmented dsRNA reovirus by transfecting cells with a combination of synthetic ssRNA, dsRNA, *in vitro* translated reovirus products, and complemented with a helper virus of different serotype (Roner, M.R., et al., *Virology*, 179, 845-852 (1990)). The resulting virus was discriminated from the helper virus by plaque assay. However, in this system the use of a helper virus was necessary. In contrast, the presently described reverse genetics system of IBDV does not require a helper virus or other viral proteins. Transfection of cells with plus-sense RNAs of both segments was sufficient to generate infectious virus (IBDV). The fate of the additional one or four nucleotides, respectively, transcribed at the 3'-end of segment A was not determined. However, this did not prevent the replication of the viral dsRNA. Similar effects were observed for plus-stranded RNA viruses by different investigators (Boyer, J.C., et al., *Virology*, 198, 415-426 (1994)).

Transfection of plus-sense RNAs of both segments into the same cell was necessary for the successful recovery of IBDV. Transfected RNAs of both segments had to be translated by the cellular translation machinery. The polyprotein of segment A was presumably processed into VP2, VP3 and VP4 proteins which form the viral capsid. The translated protein VP1 of segment B probably acted as a RNA-dependent RNA polymerase and transcribed minus-strands from synthetic plus-strands of both segments, and the reaction products formed dsRNA. Recently, Dobos reported that *in vitro* transcription by the virion RNA-dependent RNA polymerase of infectious pancreatic necrosis virus (IPNV), a prototype virus of the *Birnaviridae* family, is primed by VP1 and then proceeds via an asymmetric, semiconservative, strand-displacement mechanism to synthesize only plus strands during replication of the viral genome (Dobos, P., *Virology*, 208, 10-25 (1995)). The present system shows that synthesis of minus-strands proceeds on the plus-strands. Whether the resulting transcribed minus-strand RNA serves as a template for the transcription of plus-strands or not remains the subject of further investigation.

To prove that the infectious IBDV contained in the supernatants of transfected cells was indeed derived from the synthetic transcripts, an artificial chimera was generated containing segment A of a serotype II strain and segment B of a serotype I strain. Sequence analysis verified this genome combination. The results also indicate that the terminal sequence motifs described by Mundt and Müller are probably responsible for replication, sorting and packaging of the viral genome (Mundt, E. et al., *Virology*, 209, 10-18 (1995)). Presence of serotype-specific terminal sequences obviously does not prevent proper replication of serotype II A segment by the action of the RNA-dependent RNA polymerase VP1 of the serotype I segment B. The ability to create recombinant viruses will greatly help in analyzing the precise function of serotype-specific and serotype-common terminal sequences.

The recovery of infectious IBDV demonstrates that only the plus-strand RNAs of both segments are sufficient to initiate replication of dsRNA. Thus, the results are in agreement with the general features of reovirus and rotavirus replication where the plus-strand RNAs serve as a template for the synthesis of progeny minus-strands to yield dsRNA (Schonberg, M., et al., *Proc. Natl. Acad. Sci.* Patton, J.T., *Virus Res.*, 6, 217-233 (1986); Chen, D., et al., *J. Virol.*, 68, 7030-7039 (1994)). However, the semiconservative, strand displacement mechanisms proposed by Spies et al. and Dobos could not be excluded (Spies, U., et al., *Virus Res.*, 8, 127-140 (1987); Dobos, P., *Virology*, 208, 10-25 (1995)). The development of a reverse genetics system for IBDV will greatly facilitate future studies of gene expression, pathogenesis, and help in the design of new generations of live and inactivated IBDV vaccines.

As used in the present application, the term "synthetic" as applied to nucleic acids indicates that it is a man made nucleic acid in contrast to a naturally occurring nucleic acid. The term implies no limitation as to the method of manufacture, which can be chemical or biological as long as the method of manufacture involves the intervention of man.

The term "cDNA" is intended to encompass any cDNA containing segments A and B and the 5' and 3' noncoding regions of segments A and B.

The term "infectious" as applied to viruses indicates that the virus has the ability to reproduce. The virus can be pathogenic or nonpathogentic and still be infectious.

The present invention provides a system for the generation of infectious bursal disease virus using synthetic RNA transcripts. This system can be used to study the regulation of viral gene expression, pathogenesis, and for the design of a new generation of live and inactivated IBDV vaccines.

The present invention provides a recombinant vector containing at least one copy of the cDNA according to the present invention. The recombinant vector may also comprise other necessary sequences such as expression control sequences, markers, amplifying genes, signal sequences, promoters, and the like, as is known in the art. Useful vectors for this purpose are plasmids, and viruses such as baculoviruses, herpes virus (HVT) and pox viruses, e.g., fowl pox virus, and the like.

Also provided herein is a host cell transformed with the recombinant vector of the present invention or a host cell transfected with the synthetic RNA of the present invention. The host cell may be a eukaryotic or a prokaryotic host cell. Suitable examples are *E. coli*, insect cell lines such as Sf-9, chicken embryo fibroblast (CEF) cells, chicken embryo kidney (CEK) cells, African green monkey Vero cells and the like.

Also part of this invention is an IBDV poultry vaccine comprising a poultry protecting amount of a recombinantly produced virus or portion of a virus, wherein the virus is inactivated or modified such that it is no longer virulent.

The virus can be inactivated by chemical or physical means. Chemical inactivation can be achieved by treating the virus with, for example, enzymes, formaldehyde, β-propiolactone, ethylene-imine or a derivative thereof, an organic solvent (e.g. halogenated hydrocarbon) and or a detergent. If necessary, the inactivating substance can be neutralized after the virus has been inactivated. Physical inactivation can be carried out by subjecting the viruses to radiation such as UV light, X-radiation, or γ-radiation.

The virus can be attenuated by known methods including serial passage, deleting sequences of nucleic acids and site directed mutagenesis either before or after production of the infectious virus to produce a virus which retains sufficient antigenicity but which has reduced virulence.

Physiologically acceptable carriers for vaccination of poultry are known in the art and need not be further described herein. In addition to being physiologically acceptable to the poultry the carrier must not interfere with the immunological response elicited by the vaccine and/or with the expression of its polypeptide product.

Other additives, such as adjuvants and stabilizers, among others, may also be contained in the vaccine in amounts known in the art. Preferably, adjuvants such as aluminum hydroxide, aluminum phosphate, plant and animal oils, and the like, are administered with the vaccine in amounts sufficient to enhance the immune response to the IBDV. The amount of adjuvant added to the vaccine will vary depending on the nature of the adjuvant, generally ranging from about 0.1 to about 100 times the weight of the IBDV, preferably from about 1 to about 10 times the weight of the IBDV.

The vaccine of the present invention may also contain various stabilizers. Any suitable stabilizer can be used including carbohydrates such as sorbitol, mannitol, starch, sucrose, dextrin, or glucose; proteins such as albumin or casein; and buffers such as alkaline metal phosphate and the like. A stabilizer is particularly advantageous when a dry vaccine preparation is prepared by lyophilization.

The vaccine can be administered by any suitable known method of inoculating poultry including nasally, ophthalmically, by injection, in drinking water, in the feed, by exposure, and the like. Preferably, the vaccine is administered by mass administration techniques such as by placing the vaccine in drinking water or by spraying the animals' environment. When administered by injection, the vaccines are preferably administered parenterally. Parenteral administration as used herein means administration by intravenous, subcutaneous, intramuscular, or intraperitoneal injection.

The vaccine of the present invention is administered to poultry to prevent IBD anytime before or after hatching. Preferably, the vaccine is administered prior to the time of birth and after the animal is about 6 weeks of age. Poultry is defined to include but not be limited to chickens, roosters, hens, broilers, roasters, breeders, layers, turkeys and ducks.

The vaccine may be provided in a sterile container in unit form or in other amounts. It is preferably stored frozen, below -20°C, and more preferably below -70°C. It is thawed prior to use, and may be refrozen immediately thereafter. For administration to poultry the recombinantly produced virus may be suspended in a carrier in an amount of about 10^4 to 10^7 pfu/ml, and more preferably about 10^5 to 10^6 pfu/ml in a carrier such as a saline solution. The inactivated vaccine may contain the antigenic equivalent of 10^4 to 10^7 pfu/ml suspended in a carrier. Other carriers may also be utilized as is known in the art. Examples of pharmaceutically acceptable carriers are diluents and inert pharmaceutical carriers known in the art. Preferably, the carrier or diluent is one compatible with the administration of the vaccine by mass administration techniques. However, the carrier or diluent may also be compatible with other administration methods such as injection, eye drops, nose drops, and the like.

The invention also can be used to produce combination vaccines with the IBDV material. The IBDV material can be combined with antigen material of Newcastle Disease Virus Infectious Bronchitis virus, Reo virus, Adeno virus and/or the Marek virus.

The foregoing embodiments of the present invention are further described in the following Examples. However, the present invention is not limited by the Examples, and variations will be apparent to those skilled in the art without departing from the scope of the present invention.

<u>Brief Description of the Drawings</u>

Figure 1 is a schematic diagram of cDNA constructs used for synthesis of plus-sense ssRNAs of IBDV with T7 RNA polymerase. Construct pUC19FLAD78 contains the cDNA of segment A of IBDV strain D78 and the recombinant plasmid pUC18FLA23 contains the full-length cDNA of segment

A of IBDV strain 23/82. Segment A of IBDV encodes the polyprotein (VP2-VP4-VP3), and the recently identified VP5 protein. Plasmid pUC18FLBP2 contains the cDNA of segment B of strain P2 which encodes the RNA-dependent RNA polymerase (VP1). Virus specific sequences are underlined and the T7 promoter sequences are italicized. Restriction sites are shown in boldface and identified. The cleavage sites of the linearized plasmids are shown by vertical arrows and the transcription directions are marked by horizontal arrows.

Figure 2 shows an agarose gel analysis of the transcription reaction products that were used for transfection of Vero cells. Synthetic RNAs transcribed *in vitro* using T7 RNA polymerase and linearized plasmids pUC19FLAD78 (lanes 2, 4 and 6) containing the cDNA of segment A of IBDV strain D78, and pUC18FLBP2 (lanes 1, 3 and 5) containing the cDNA of segment B of strain P2, respectively. After transcription, the reaction mixtures were either treated with DNase (lanes 1 and 2), RNase (lanes 3 and 4) or left untreated (lanes 5 and 6). Two µl of the reaction products were analyzed on 1% agarose gel. Lambda DNA, digested with *Hin*d III/*Eco*R I, was used as markers (lane M).

Figure 3 shows a comparison of nucleotide sequences of cloned RT-PCR fragments from segments A and B of the chimeric IBDV strain 23A/P2B (bold-typed) with known sequences of segments A and B of serotype II strain 23/82 and serotype I strain P2, respectively. Nucleotide identities are marked by a colon.

Figure 4 shows the DNA sequence of pUC18FLA23.

Figure 5 shows the DNA sequence of pUC19FLAD78.

Figure 6 shows the DNA sequence of pUC18FLBP2.

EXAMPLES

Viruses and Cells. Two serotype I strains of IBDV, the attenuated P2 strain from Germany and the vaccine strain D78 (Intervet International), and one serotype II strain, the apathogenic 23/82 strain, were propagated in chicken embryo cells (CEC) and purified (Mundt, E. et al., *Virology*, 209, 10-18 (1995); Vakharia, V.N., et al., *Virus Res.*, 31, 265-273 (1994)). Vero cells

were grown in M199 medium supplemented with 5% fetal calf serum (FCS) and used for transfection experiments. Further propagation of the recovered virus and immunofluorescence studies were carried out in Vero cells (Mundt, E., et al., *J. Gen. Virol.*, 76, 437-443, (1995)). For plaque assay, monolayers of secondary CEC were prepared and used (Müller, H., et al., *Virus Res.*, 4, 297-309 (1986)).

Construction of Full-Length cDNA Clones of IBDV genome. Full-length cDNA clones of IBDV segments A and B were independently prepared. The cDNA clones containing the entire coding region of the RNA segment A of strain D78 were prepared using standard cloning procedures and methods (Vakharia, V.N., et al., *Virus Res.*, 31, 265-273 (1994)). By comparing the D78 terminal sequences with recently published terminal sequences of other IBDV strains (Mundt, E. et al., *Virology*, 209, 10-18 (1995)), it was observed that D78 cDNA clones lacked the conserved first 17 and last 10 nucleotides at the 5'- and 3'-ends, respectively. Therefore, to construct a full-length cDNA clone of segment A, two primer pairs (A5'-D78, A5-IPD78 and A3'-IPD78) were synthesized and used for PCR amplification (Table 1). The DNA segments were amplified according to the protocol of the supplier (New England Biolabs) using "Deep Vent Polymerase" (high fidelity thermophilic DNA polymerase). Amplified fragments were cloned into the *Eco*R I site of a pCRII vector (Invitrogen Corp.) to obtain plasmids pCRD78A5' and pCRD78A3', respectively. Each plasmid was digested with *Eco*R I and *Sal* I and the resultant fragments were ligated into *Eco*R I digested pUC19 to obtain plasmid pUC19FLAD78 (SEQ ID NOS:27 AND 29) which now contains a full-length cDNA copy of segment A encoding all the structural proteins (VP2, VP4 and VP3, SEQ ID NO:30) as well as the non-structural VP5 protein (SEQ ID NO:28) (Fig. 1).

Two primer pairs (A5'-23, A5IP23 and A3'-23, A3-IP23; see Table 1) were used for reverse transcription (RT) of viral genomic dsRNA of strain 23/82 using "SuperScript RT II" (RNA directed DNA polymerase with reduced RNase H activity, GIBCO/BRL). The RT reaction products were purified by phenol/chloroform extraction and ethanol precipitation. To obtain two cDNA

fragments bounded by primer pairs A5'-23, A5-IP23 and A3'-23, A3-IP23, respectively, RT reaction products were amplified by PCR using "Deep Vent polymerase". Both RT and PCR were carried out according to the supplier's protocol. Resulting PCR fragments were blunt-end ligated into *Sma* I cleaved pUC18 vector to obtain pUC23A5' and pUC23A3'. The 3'-end of segment A contained in plasmid pUC23A3' was ligated into the *Hin*d III-*Bst*B I cleaved plasmid pUC23A5' to establish the full-length cDNA of segment A of strain 23/82. The resulting plasmid was termed pUC18FLA23 (SEQ ID NOS: 31 AND 33)(Fig. 1) and encodes structural proteins VP2, VP3 and VP4 (SEQ ID NO: 32) and non-structural protein VP5 (SEQ ID NO: 34)

To obtain cDNA clones of segment B of P2 strain, two primer pairs (B5'-P2, B5-IPP2 and B3'-P2, B3-IPP2) were designed according to the published sequences and used for RT-PCR amplification (see Table 1). Using genomic dsRNA as template, cDNA fragments were synthesized and amplified according to the supplier's protocol (Perkin-Elmer Cetus). Amplified fragments were blunt-end ligated into *Sma* I cleaved pBS vector (Stratagene) to obtain clones pBSP2B5' and pBSP2B3'. To construct a full-length clone of segment B, the 5'-end fragment of plasmid pBSP2B5' was first subcloned between *Eco*R I and *Pst* I sites of pUC18 vector to obtain pUCP2B5'. Then the 3'-end fragment of plasmid pBSP2B3' was inserted between the unique *Bgl* II and *Pst* I sites of plasmid pUCP2B5' to obtain a full-length plasmid pUC18FLBP2 (SEQ ID NO:25) which encodes the VP1 protein (SEQ ID NO: 26) (Fig. 1). Plasmids pUC18FLBP2, pUC18FLA23 and pUC19FLAD78 were completely sequenced by using the "Sequenase" DNA sequencing system (U.S. Biochem.), and the sequence data were analyzed using either "DNASIS" (Pharmacia) or "PC/Gene" (Intelligenetics) software. The integrity of the full-length constructs was tested by *in vitro* transcription and translation coupled reticulocyte lysate system using T7 RNA polymerase (Promega).

Transcription and Transfection of Synthetic RNAs. Plasmids pUC19FLAD78, pUC18FLA23 and pUC18FLBP2 were digested with *Bsr*G I, *Nsi* I and *Pst* I enzymes (see Fig. 1), respectively, and used as templates for *in vitro* transcription with T7 RNA polymerase (Promega). Briefly, restriction

enzyme cleavage assays were adjusted to 0.5% SDS and incubated with proteinase K (0.5 mg/ml) for 1 hour at 37°C. The linearized DNA templates (~3 μg) were recovered after ethanol precipitation, and were added separately to a transcription reaction mixture (50 μl) containing 40 mM Tris-HCl (pH 7.9), 10 mM NaCl, 6 mM $MgCl_2$, 2 mM spermidine, 0.5 mM ATP, CTP and UTP each, 0.1 mM GTP, 0.25 mM cap analog [m7G(5') PPP(5') G], 120 units of "RNasin" (ribonuclease inhibitor), 150 units T7 RNA polymerase (Promega), and incubated at 37°C for 1 hour. Synthetic RNA transcripts were purified by phenol/chloroform extraction and ethanol precipitation. As controls, the transcription products were treated with either DNase or RNase (Promega) before the purification step.

Vero cells were grown to 80% confluence in 60 mm dishes and washed once with phosphate-buffered saline (PBS). Three ml of "OPTI-MEM I" (reduced serum medium containing HEPES buffer, sodium bicarbonate, hypoxanthine, thymidine, sodium pyruvate, L-glutamine, trace elements, growth factors and phenol red; from GIBCO/BRL) were added to the monolayers, and the cells were incubated at 37°C for 1 hour in a CO_2 incubator. Simultaneously, 0.15 ml of "OPTI-MEM I" was incubated with 1.25 μg of "Lipofectin" reagent (N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride and dioleoylphosphatidylethanolamine, GIBCO/BRL) for 45 min. in a polystyrene tube at room temperature. Synthetic RNA transcripts of both segments, resuspended in 0.15 ml of diethyl pyrocarbonate-treated water, were added to the OPTI-MEM-Lipofectin-mixture, mixed gently, and incubated on ice for 5 min. After removing the "OPTI-MEM" from the monolayers in 60 mm dishes and replacing with fresh 1.5 ml of "OPTI-MEM", the nucleic acid containing mixture was added drop-wise to the Vero cells and swirled gently. After 2 hours of incubation at 37°C, the mixture was replaced with M199 medium [$CaCl_2$ (annhydrous), $Fe(NO_3)_3$ $9H_20$, KCl, $MgSO_4$ (anhydrous), NaCl, $NaH_2PO_4H_2O$, $NaHCO_3$, L-Alanine, L-Arginine HCl, L-Aspartic acid, L-Cysteine HCl H_2O, L-Cysteine 2HCl, L-Glutamic acid, L-Glutamine, Glycine, L-Histidine HCL H_2O, L-Hydroxyproline, L-Isoleucine, L-Leucine, L-Lysine HCl, L-Methionine, L-Phenylalanine, L-

Proline, L-Serine, L-Threonine, L-Tryptophan, L-Tyrosine 2Na $2H_2O$, L-Valine, Alpha tocopherol PO_4 Na_2, Ascorbic Acid, Biotin, Calciferol, D-Calcium pantothenate, Choline chloride, Folic acid, I-Inositol, Menandione $NaHSO_3$ $3H_2O$, Niacin, Nicotinamide, Para-aminobenzoic acid, Pyridoxine HCl, Riboflavin, Thiamine HCl, Vitamin A Acetate, Adenine SO_4, Adenylic Acid, ATP, Na_2, Cholesterol, 2-Deoxy-D-Ribose, D-Glucose, Glutathione, Guanine HCl, Hypoxanthine Na, Phenol Red Na, Ribose, Sodium Acetate (anhydrous), Thymine, Tween 80, Uracil,and Xanthine Na; from Mediatech, Inc.] containing 5% FCS (without rinsing cells) and the cells were further incubated at 37°C for desired time intervals.

Identification of Generated IBDV. CEC were infected with filtered (0.2 µm) supernatant from Vero cells transfected with transcripts of pUC18FLA23 and pUC18FLP2B. 16 hours post-infection, the whole cell nucleic acids were isolated (Mundt, E. et al., *Virology*, 209, 10-18 (1995)). Primers were designed according to the published sequences and RT-PCR fragments were amplified, cloned and sequenced (Mundt, E. et al., *Virology*, 209, 10-18 (1995)). Sequence data were analyzed by using "DNASIS" software.

Immunofluorescence. Vero cells, grown on cover slips to 80% confluence, were infected with the supernatants derived from transfected Vero cells (after freeze-thawing) and incubated at 37°C for two days. The cells were then washed, fixed with acetone and treated with polyclonal rabbit anti-IBDV serum. After washing, the cells were treated with fluorescein labeled goat-anti-rabbit antibody (Kirkegaard & Perry Lab.) and examined by fluorescence microscope.

Plaque Assay. Monolayers of secondary CEC, grown in 60 mm dishes, were inoculated with the supernatants derived from transfected Vero cells. After 1 hour of infection, the cells were washed once with PBS and overlayed with 0.8% Agar noble (Difco) containing 10% tryptose phosphate broth, 2% FCS, 0.112% $NaHCO_3$, 10^3 units penicillin, 10^3 µg/ml streptomycin, 0.25 µg/ml fungizone, 0.005% neutral red, 0.0015% phenol red. The cells

were incubated at 37°C for 2 to 3 days until plaques could be observed and counted (Müller, H., et al., *Virus Res.*, 4, 297-309 (1986)).

Construction of Full-Length cDNA clones of IBDV Genome. To develop a reverse genetics system for the dsRNA virus IBDV, two independent cDNA clones were constructed that contain segment A of strain D78 and segment B of strain P2 (Fig. 1). Each plasmid encoded either the precursor of structural proteins (VP2, VP4, VP3) and VP5 or only VP1 protein (RNA-dependent RNA polymerase). Plasmid pUC18FLBP2 upon digestion with *Pst* I and transcription *in vitro* by T7 RNA polymerase, would yield RNA containing the correct 5'- and 3'-ends. Whereas, upon digestion with *Bsr*G I and transcription, plasmid pUC19FLAD78 would yield RNA containing the correct 5'-end but with additional four nucleotides at the 3'end. Coupled transcription and translation of the above plasmids in a rabbit reticulocyte system yielded protein products that were correctly processed and comigrated with the marker IBDV proteins after fractionating on SDS-polyacrylamide gel and autoradiography (data not shown).

Transcription, Transfection and Generation of Infectious Virus. Plus-sense transcripts of IBDV segment A and B were synthesized separately *in vitro* with T7 RNA polymerase using linearized full-length cDNA plasmids as templates (see Fig. 2). Although two species of RNA transcripts were observed for segment B on a neutral gel (lanes 1 and 5), fractionation of these samples on a denaturing gel yielded only one transcript-specific band (data not shown). In order to show that plus-sense RNA transcripts of both segments are needed for the generation of infectious virus, the transcription mixtures were incubated with different nucleases, as shown in Fig. 2. Synthetic RNAs recovered after treating the transcription products with DNase (lanes 1+2), RNase (lanes 3+4) or without treatment (lanes 5+6), were used for the transfection of Vero cells. As mock control, Lipofectin alone was used. Five days post-transfection, cytopathic effect (CPE) was only visible in Vero cells transfected with combined transcripts of untreated or DNase-treated transcription products, but not with RNase-treated transcription mixtures or

mock-transfected control. In addition, no CPE was detected when Vero cells were transfected with RNA of only segment A or B (data not shown). These results demonstrate that replication of IBDV ensued after transfection of Vero cells with plus-sense ssRNAs of both segments of IBDV. To verify that the agent causing the CPE in Vero cells was indeed IBDV, transfected Vero cells were freeze-thawed, and supernatants were clarified by centrifugation, and used to infect CEC or Vero cells. CEC infected with the supernatants derived from Vero transfected cells of untreated or DNase-treated transcription mixtures produced CPE in one day post-inoculation (Table 2). However, no CPE could be detected even after five days in CEC, with the supernatants from transfected Vero cells of RNase-treated transcription mixtures, untreated segment A or B transcription mixtures and mock-transfected Vero cells. Similarly, when Vero cells on cover slips were infected with the same supernatants as described above and examined by immunofluorescence staining after 2 days, only supernatants derived from transfected Vero cells of untreated or DNAse-treated transcription mixtures gave positive immunofluorescence signal (Table 2).

Recovery of Transfectant Virus. To determine the time point for the recovery of infectious virus, Vero cells were transfected with combined RNA transcripts of segments A and B. At 4, 8, 16, 24, 36 and 48 hours post-transfection, the supernatants were examined for the presence of transfectant virus by infectivity and plaque assays, as shown in Table 3. Our results indicate that the virus could be recovered as early as 36 hours after transfection. Virus titer was 2.3 x 10^2 pfu/ml which appear to drop for samples obtained later than 48 hours after transfection.

Generation of a Chimeric Virus. To prove that plus-sense ssRNA of both segments of IBDV are sufficient for recovery of infectious virus, a chimeric IBDV was generated. Plasmid pUC18FLA23 containing a full-length sequence of segment A of serotype II strain was linearized by *Nsi* I digestion and ssRNA was synthesized *in vitro* using T7 RNA polymerase. The ssRNA transcript specifies the correct 5'-end but contains one additional residue at the 3'-end (Fig. 1). Vero cells were transfected with ssRNA of segment A of

serotype II strain 23/82 and ssRNA of segment B of serotype I strain P2. Five days after transfection when CPE was evident, the supernatant was clarified (after freeze-thawing) and used to infect CEC. After a second passage in CEC, genomic RNA of the virus was analyzed by RT-PCR and sequencing of the PCR products. Primers for segment A were deigned to specifically amplify only segment A sequences derived from the serotype II strain. Primer for segment B bound to sequences of both serotypes. The amplified fragments were cloned and sequenced. The obtained segment A sequences showed a perfect match with known segment A sequences of serotype II strain 23/82, whereas segment B sequence exhibited complete homology to published segment B sequences of serotype I strain P2 (Fig. 3).

Table 1. Oligonucleotides Used for the Construction of Full Length cDNA Clones of IBDV Genomic Segments A and B.

Nucleotide Sequence	Orientation	Name	Nucleotide Number
*TAATACGACTCACTATA*GGATACGATCGGTCTGACCCCGGGGGAGTCA	(+)	A5'-D78	1-31
AGA**GAATTC***TAATACGACTCACTATA*GGATACGATCGGTCTGAC	(+)	A5'-23	1-48
TGTACAGGGGACCCGCGAACGGATCCAATT	(-)	A3'-D78	3237-3261
CGGC**GAATTCATGCAT**AGGGGACCCGCGAACGGATC	(-)	A3'-23	3242-3261
CGTCGACTACGGGATTCTGG	(-)	A5-IPD78	1711-1730
CAGAGGCAGTACTCCGTCTG	(-)	A5-IP23	1971-1990
A**GTCGAC**GGGATTCTTGCTT	(+)	A3-IPD78	1723-1742
GAAGGTGTGCGAGAGGAC	(+)	A3-IP23	1883-1900
AGA**GAATTC***TAATACGACTCACTATA*GGATACGATGGGTCTGAC	(+)	B5'-P2	1-18
CGATCTG**CTGCAG**GGGGCCCCCGCAGGCGAAGG	(-)	B3'-P2	2807-2827
CTTGAGACTCTTGTTCTCTACTCC	(-)	B5-IPP2	1915-1938
ATACAGCAAAGATCTCGGG	(+)	B3-IPP2	1839-1857

Composition and location of the oligonucleotide primers used for cloning. T7 promoter sequences are marked with italic types, the virus specific sequences are underlined, and the restriction sites marked in boldface. Orientation of the virus specific sequence of the primer is shown for sense (+) and antisense (-). The positions where the primers bind (nucleotide number) are according to the published sequences of P2 strain (2).

Table 2. Generation of Infections IBDV From Synthetic RNAs of Segment A and B.

Material Transfected	CPE	Immunofluoroescence
ssRNA A+B, DNase-treated	+	+
ssRNA A+B, RNase-treated	-	-
ssRNA A+B, untreated	+	+
ssRNA A, untreated	-	-
ssRNA B, untreated	-	-
Lipofectin only	-	-

Vero cells were transfected with synthetic RNAs of segment A and B derived from transcription reactions that were either untreated or treated with DNase or RNase. After 5 days, the supernatants were collected, clarified by centrifugation, and analyzed for the presence of virus. The infectivity of the recovered virus was determined in CEC by the appearance of cytopathic effect (CPE) 1-2 days post-inoculation. The specificity of the recovered virus was determined by immunofluorescence staining of infected Vero cells with rabbit anti-IBDV serum.

Table 3. Recovery of Virus at Various Times Post-Transfection.

Time in hours post-transfection	CPE	Immunofluorescence	pfu/ml
4	-	-	0
8	-	-	0
16	-	-	0
24	-	-	0
36	+	+	2.3×10^2
48	+	+	6.0×10^1

Vero cells were transfected with synthetic RNAs of segment A and B as described. The infectivity and specificity of the recovered virus was detected by CPE in CEC and immunofluorescence staining in Vero cells, respectively. Monolayers of secondary CEC were used for plaque assay after inoculating the cells with the supernatants derived from transfected Vero cells. Approximate titer of the virus was calculated as plaque forming units per ml (pfu/ml).

SEQUENCE LISTING

(1) GENERAL INFORMATION:

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(ii) TITLE OF INVENTION: A METHOD FOR GENERATING BIRNAVIRUS FROM SYNTHETIC RNA TRANSCRIPTS

(iii) NUMBER OF SEQUENCES: 34

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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: US
(B) FILING DATE:
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(viii) ATTORNEY/AGENT INFORMATION:
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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GAATTCGGCT TTAATACGAC TCACTATAGG ATACGATCGG TCTGAC 46

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 41 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

AATTGGATCC GTTCGCGGGT CCCCTGTACA AAGCCGAATT C 41

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CGGCGAATTC ATGCATAGGG GACCCGCGAA CGGATC 36

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

GTCAGACCGA TCGTATCCTA TAGTGAGTCG TATTAGAATT CTCT 44

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

TTGCATGCCT GCAGGGGGCC CCCGCAGGCG AAG 33

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

TCGTATCCTA TAGTGAGTCG TATTAGAATT C 31

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GGAAGCCTGA GTGAGTTGAC TGACTACAGC TACAACGGGC TGATGTCAGC CACTGCGAAC 60

ATCAACGACA AGATCGGGAA CGTTCTAGTT GGAGAAGGGG TGACTGTTCT CAGTCTACCG 120

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

GGAAGCCTGA GTGAGTTGAC TGACTACAGC TACAACGGGC TGATGTCAGC CACTGCGAAC 60

ATCAACGACA AGATCGGGAA CGTTCTAGTT GGAGAAGGGG TGACTGTTCT CAGTCTACC 119

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GGAAGCCTGA GTGAACTGAC AGATGTTAGC TACAATGGGT TGATGTCTGC AACAGCCAAC 60

ATCAACGACA AAATTGGGAA CGTCCTAGTA GGGGAAGGGG TCACCGTCCT CAGCTTACCC 120

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

TTTTCAATAG TCCACAGGCG CGAACGAAGA TCTCAGCAGC GTTCGGCATA AAGCCTACTG 60

CTGGACAAGA CGTGGAAGAA CTCTTGATCC CCAAAGTCTG GGTGCCACCT GAGGATCCGC 120

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

TTTTCAACAG TCCACAGGCG CGAAGCACGA TCTCAGCAGC GTTCGGCATA AAGCCTACTG 60

CTGGACAAGA CGTGGAAGAA CTCTTGATCC CTAAAGTTTG GGTGCCACCT GAGGATCCGC 120

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 120 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

TTTTCAACAG TCCACAGGCG CGAAGCACGA TCTCAGCAGC GTTCGGCATA AAGCCTACTG 60

CTGGACAAGA CGTGGAAGAA CTCTTGATCC CTAAAGTTTG GGTGCCACCT GAGGATCCGC 120

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

TAATACGACT CACTATAGGA TACGATCGGT CTGACCCCGG GGGAGTCA 48

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

AGAGAATTCT AATACGACTC ACTATAGGAT ACGATCGGTC TGAC 44

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 30 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

TGTACAGGGG ACCCGCGAAC GGATCCAATT 30

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 36 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

CGGCGAATTC ATGCATAGGG GACCCGCGAA CGGATC 36

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

CGTCGACTAC GGGATTCTGG 20

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

CAGAGGCAGT ACTCCGTCTG 20

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

AGTCGACGGG ATTCTTGCTT 20

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

GAAGGTGTGC GAGAGGAC 18

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

AGAGAATTCT AATACGACTC ACTATAGGAT ACGATGGGTC TGAC 44

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 33 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CGATCTGCTG CAGGGGGCCC CCGCAGGCGA AGG 33

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

CTTGAGACTC TTGTTCTCTA CTCC 24

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

ATACAGCAAA GATCTCGGG 19

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2827 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 112..2745

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

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GGATACGATG GGTCTGACCC TCTGGGAGTC ACGAATTAAC GTGGCTACTA GGGGCGATAC      60

CCGCCGCTGG CCGCCACGTT AGTGGCTCCT CTTCTTGATG ATTCTGCCAC C ATG AGT     117
                                                         Met Ser
                                                           1

GAC ATT TTC AAC AGT CCA CAG GCG CGA AGC ACG ATC TCA GCA GCG TTC      165
Asp Ile Phe Asn Ser Pro Gln Ala Arg Ser Thr Ile Ser Ala Ala Phe
        5                  10                  15

GGC ATA AAG CCT ACT GCT GGA CAA GAC GTG GAA GAA CTC TTG ATC CCT      213
Gly Ile Lys Pro Thr Ala Gly Gln Asp Val Glu Glu Leu Leu Ile Pro
    20                  25                  30

AAA GTT TGG GTG CCA CCT GAG GAT CCG CTT GCC AGC CCT AGT CGA CTG      261
Lys Val Trp Val Pro Pro Glu Asp Pro Leu Ala Ser Pro Ser Arg Leu
35                  40                  45                  50

GCA AAG TTC CTC AGA GAG AAC GGC TAC AAA GTT TTG CAG CCA CGG TCT      309
Ala Lys Phe Leu Arg Glu Asn Gly Tyr Lys Val Leu Gln Pro Arg Ser
                55                  60                  65

CTG CCC GAG AAT GAG GAG TAT GAG ACC GAC CAA ATA CTC CCA GAC TTA      357
Leu Pro Glu Asn Glu Glu Tyr Glu Thr Asp Gln Ile Leu Pro Asp Leu
            70                  75                  80

GCA TGG ATG CGA CAG ATA GAA GGG GCT GTT TTA AAA CCC ACT CTA TCT      405
Ala Trp Met Arg Gln Ile Glu Gly Ala Val Leu Lys Pro Thr Leu Ser
        85                  90                  95

CTC CCT ATT GGA GAT CAG GAG TAC TTC CCA AAG TAC TAC CCA ACA CAT      453
Leu Pro Ile Gly Asp Gln Glu Tyr Phe Pro Lys Tyr Tyr Pro Thr His
    100                 105                 110

CGC CCT AGC AAG GAG AAG CCC AAT GCG TAC CCG CCA GAC ATC GCA CTA      501
Arg Pro Ser Lys Glu Lys Pro Asn Ala Tyr Pro Pro Asp Ile Ala Leu
115                 120                 125                 130
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CTC AAG CAG ATG ATT TAC CTG TTT CTC CAG GTT CCA GAG GCC AAC GAG     549
Leu Lys Gln Met Ile Tyr Leu Phe Leu Gln Val Pro Glu Ala Asn Glu
                135                 140                 145

GGC CTA AAG GAT GAA GTA ACC CTC TTG ACC CAA AAC ATA AGG GAC AAG     597
Gly Leu Lys Asp Glu Val Thr Leu Leu Thr Gln Asn Ile Arg Asp Lys
            150                 155                 160

GCC TAT GGA AGT GGG ACC TAC ATG GGA CAA GCA AAT CGA CTT GTG GCC     645
Ala Tyr Gly Ser Gly Thr Tyr Met Gly Gln Ala Asn Arg Leu Val Ala
        165                 170                 175

ATG AAG GAG GTC GCC ACT GGA AGA AAC CCA AAC AAG GAT CCT CTA AAG     693
Met Lys Glu Val Ala Thr Gly Arg Asn Pro Asn Lys Asp Pro Leu Lys
    180                 185                 190

CTT GGG TAC ACT TTT GAG AGC ATC GCG CAG CTA CTT GAC ATC ACA CTA     741
Leu Gly Tyr Thr Phe Glu Ser Ile Ala Gln Leu Leu Asp Ile Thr Leu
195                 200                 205                 210

CCG GTA GGC CCA CCC GGT GAG GAT GAC AAG CCC TGG GTG CCA CTC ACA     789
Pro Val Gly Pro Pro Gly Glu Asp Asp Lys Pro Trp Val Pro Leu Thr
                215                 220                 225

AGA GTG CCG TCA CGG ATG TTG GTG CTG ACG GGA GAC GTA GAT GGC GAC     837
Arg Val Pro Ser Arg Met Leu Val Leu Thr Gly Asp Val Asp Gly Asp
            230                 235                 240

TTT GAG GTT GAA GAT TAC CTT CCC AAA ATC AAC CTC AAG TCA TCA AGT     885
Phe Glu Val Glu Asp Tyr Leu Pro Lys Ile Asn Leu Lys Ser Ser Ser
        245                 250                 255

GGA CTA CCA TAT GTA GGT CGC ACC AAA GGA GAG ACA ATT GGC GAG ATG     933
Gly Leu Pro Tyr Val Gly Arg Thr Lys Gly Glu Thr Ile Gly Glu Met
    260                 265                 270

ATA GCT ATC TCA AAC CAG TTT CTC AGA GAG CTA TCA ACA CTG TTG AAG     981
Ile Ala Ile Ser Asn Gln Phe Leu Arg Glu Leu Ser Thr Leu Leu Lys
275                 280                 285                 290

CAA GGT GCA GGG ACA AAG GGG TCA AAC AAG AAG AAG CTA CTC AGC ATG    1029
Gln Gly Ala Gly Thr Lys Gly Ser Asn Lys Lys Lys Leu Leu Ser Met
                295                 300                 305

TTA AGT GAC TAT TGG TAC TTA TCA TGC GGG CTT TTG TTT CCA AAG GCT    1077
Leu Ser Asp Tyr Trp Tyr Leu Ser Cys Gly Leu Leu Phe Pro Lys Ala
            310                 315                 320

GAA AGG TAC GAC AAA AGT ACA TGG CTC ACC AAG ACC CGG AAC ATA TGG    1125
Glu Arg Tyr Asp Lys Ser Thr Trp Leu Thr Lys Thr Arg Asn Ile Trp
        325                 330                 335
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TCA GCT CCA TCC CCA ACA CAC CTC ATG ATC TCT ATG ATC ACC TGG CCC      1173
Ser Ala Pro Ser Pro Thr His Leu Met Ile Ser Met Ile Thr Trp Pro
    340                 345                 350

GTG ATG TCC AAC AGC CCA AAT AAC GTG TTG AAC ATT GAA GGG TGT CCA      1221
Val Met Ser Asn Ser Pro Asn Asn Val Leu Asn Ile Glu Gly Cys Pro
355                 360                 365                 370

TCA CTC TAC AAA TTC AAC CCG TTC AGA GGA GGG TTG AAC AGG ATC GTC      1269
Ser Leu Tyr Lys Phe Asn Pro Phe Arg Gly Gly Leu Asn Arg Ile Val
                375                 380                 385

GAG TGG ATA TTG GCC CCG GAA GAA CCC AAG GCT CTT GTA TAT GCG GAC      1317
Glu Trp Ile Leu Ala Pro Glu Glu Pro Lys Ala Leu Val Tyr Ala Asp
            390                 395                 400

AAC ATA TAC ATT GTC CAC TCA AAC ACG TGG TAC TCA ATT GAC CTA GAG      1365
Asn Ile Tyr Ile Val His Ser Asn Thr Trp Tyr Ser Ile Asp Leu Glu
        405                 410                 415

AAG GGT GAG GCA AAC TGC ACT CGC CAA CAC ATG CAA GCC GCA ATG TAC      1413
Lys Gly Glu Ala Asn Cys Thr Arg Gln His Met Gln Ala Ala Met Tyr
    420                 425                 430

TAC ATA CTC ACC AGA GGG TGG TCA GAC AAC GGC GAC CCA ATG TTC AAT      1461
Tyr Ile Leu Thr Arg Gly Trp Ser Asp Asn Gly Asp Pro Met Phe Asn
435                 440                 445                 450

CAA ACA TGG GCC ACC TTT GCC ATG AAC ATT GCC CCT GCT CTA GTG GTG      1509
Gln Thr Trp Ala Thr Phe Ala Met Asn Ile Ala Pro Ala Leu Val Val
                455                 460                 465

GAC TCA TCG TGC CTG ATA ATG AAC CTG CAA ATT AAG ACC TAT GGT CAA      1557
Asp Ser Ser Cys Leu Ile Met Asn Leu Gln Ile Lys Thr Tyr Gly Gln
            470                 475                 480

GGC AGC GGG AAT GCA GCC ACG TTC ATC AAC AAC CAC CTC TTG AGC ACA      1605
Gly Ser Gly Asn Ala Ala Thr Phe Ile Asn Asn His Leu Leu Ser Thr
        485                 490                 495

CTA GTG CTT GAC CAG TGG AAC CTG ATG AGA CAG CCC AGA CCA GAC AGC      1653
Leu Val Leu Asp Gln Trp Asn Leu Met Arg Gln Pro Arg Pro Asp Ser
    500                 505                 510

GAG GAG TTC AAA TCA ATT GAG GAC AAG CTA GGT ATC AAC TTT AAG ATT      1701
Glu Glu Phe Lys Ser Ile Glu Asp Lys Leu Gly Ile Asn Phe Lys Ile
515                 520                 525                 530

GAG AGG TCC ATT GAT GAT ATC AGG GGC AAG CTG AGA CAG CTT GTC CTC      1749
Glu Arg Ser Ile Asp Asp Ile Arg Gly Lys Leu Arg Gln Leu Val Leu
                535                 540                 545
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CTT GCA CAA CCA GGG TAC CTG AGT GGG GGG GTT GAA CCA GAA CAA TCC 1797
Leu Ala Gln Pro Gly Tyr Leu Ser Gly Gly Val Glu Pro Glu Gln Ser
550 555 560

AGC CCA ACT GTT GAG CTT GAC CTA CTA GGG TGG TCA GCT ACA TAC AGC 1845
Ser Pro Thr Val Glu Leu Asp Leu Leu Gly Trp Ser Ala Thr Tyr Ser
565 570 575

AAA GAT CTC GGG ATC TAT GTG CCG GTG CTT GAC AAG GAA CGC CTA TTT 1893
Lys Asp Leu Gly Ile Tyr Val Pro Val Leu Asp Lys Glu Arg Leu Phe
580 585 590

TGT TCT GCT GCG TAT CCC AAG GGA GTA GAG AAC AAG AGT CTC AAG TCC 1941
Cys Ser Ala Ala Tyr Pro Lys Gly Val Glu Asn Lys Ser Leu Lys Ser
595 600 605 610

AAA GTC GGG ATC GAG CAG GCA TAC AAG GTA GTC AGG TAT GAG GCG TTG 1989
Lys Val Gly Ile Glu Gln Ala Tyr Lys Val Val Arg Tyr Glu Ala Leu
615 620 625

AGG TTG GTA GGT GGT TGG AAC TAC CCA CTC CTG AAC AAA GCC TGC AAG 2037
Arg Leu Val Gly Gly Trp Asn Tyr Pro Leu Leu Asn Lys Ala Cys Lys
630 635 640

AAT AAC GCA GGC GCC GCT CGG CGG CAT CTG GAG GCC AAG GGG TTC CCA 2085
Asn Asn Ala Gly Ala Ala Arg Arg His Leu Glu Ala Lys Gly Phe Pro
645 650 655

CTC GAC GAG TTC CTA GCC GAG TGG TCT GAG CTG TCA GAG TTC GGT GAG 2133
Leu Asp Glu Phe Leu Ala Glu Trp Ser Glu Leu Ser Glu Phe Gly Glu
660 665 670

GCC TTC GAA GGC TTC AAT ATC AAG CTG ACC GTA ACA TCT GAG AGC CTA 2181
Ala Phe Glu Gly Phe Asn Ile Lys Leu Thr Val Thr Ser Glu Ser Leu
675 680 685 690

GCC GAA CTG AAC AAG CCA GTA CCC CCC AAG CCC CCA AAT GTC AAC AGA 2229
Ala Glu Leu Asn Lys Pro Val Pro Pro Lys Pro Pro Asn Val Asn Arg
695 700 705

CCA GTC AAC ACT GGG GGA CTC AAG GCA GTC AGC AAC GCC CTC AAG ACC 2277
Pro Val Asn Thr Gly Gly Leu Lys Ala Val Ser Asn Ala Leu Lys Thr
710 715 720

GGT CGG TAC AGG AAC GAA GCC GGA CTG AGT GGT CTC GTC CTT CTA GCC 2325
Gly Arg Tyr Arg Asn Glu Ala Gly Leu Ser Gly Leu Val Leu Leu Ala
725 730 735

ACA GCA AGA AGC CGT CTG CAA GAT GCA GTT AAG GCC AAG GCA GAA GCC 2373
Thr Ala Arg Ser Arg Leu Gln Asp Ala Val Lys Ala Lys Ala Glu Ala
740 745 750

GAG AAA CTC CAC AAG TCC AAG CCA GAC GAC CCC GAT GCA GAC TGG TTC 2421
Glu Lys Leu His Lys Ser Lys Pro Asp Asp Pro Asp Ala Asp Trp Phe
755 760 765 770

GAA AGA TCA GAA ACT CTG TCA GAC CTT CTG GAG AAA GCC GAC ATC GCC 2469
Glu Arg Ser Glu Thr Leu Ser Asp Leu Leu Glu Lys Ala Asp Ile Ala
775 780 785

AGC AAG GTC GCC CAC TCA GCA CTC GTG GAA ACA AGC GAC GCC CTT GAA 2517
Ser Lys Val Ala His Ser Ala Leu Val Glu Thr Ser Asp Ala Leu Glu
790 795 800

GCA GTT CAG TCG ACT TCC GTG TAC ACC CCC AAG TAC CCA GAA GTC AAG 2565
Ala Val Gln Ser Thr Ser Val Tyr Thr Pro Lys Tyr Pro Glu Val Lys
805 810 815

AAC CCA CAG ACC GCC TCC AAC CCC GTT GTT GGG CTC CAC CTG CCC GCC 2613
Asn Pro Gln Thr Ala Ser Asn Pro Val Val Gly Leu His Leu Pro Ala
820 825 830

AAG AGA GCC ACC GGT GTC CAG GCC GCT CTT CTC GGA GCA GGA ACG AGC 2661
Lys Arg Ala Thr Gly Val Gln Ala Ala Leu Leu Gly Ala Gly Thr Ser
835 840 845 850

AGA CCA ATG GGG ATG GAG GCC CCA ACA CGG TCC AAG AAC GCC GTG AAA 2709
Arg Pro Met Gly Met Glu Ala Pro Thr Arg Ser Lys Asn Ala Val Lys
855 860 865

ATG GCC AAA CGG CGG CAA CGC CAA AAG GAG AGC CGC TAACAGCCAT 2755
Met Ala Lys Arg Arg Gln Arg Gln Lys Glu Ser Arg
870 875

GATGGGAACC ACTCAAGAAG AGGACACTAA TCCCAGACCC CGTATCCCCG GCCTTCGCCT 2815

GCGGGGGCCC CC 2827

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 878 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Met Ser Asp Ile Phe Asn Ser Pro Gln Ala Arg Ser Thr Ile Ser Ala
1 5 10 15

Ala Phe Gly Ile Lys Pro Thr Ala Gly Gln Asp Val Glu Glu Leu Leu

20 25 30

Ile Pro Lys Val Trp Val Pro Pro Glu Asp Pro Leu Ala Ser Pro Ser
35 40 45

Arg Leu Ala Lys Phe Leu Arg Glu Asn Gly Tyr Lys Val Leu Gln Pro
50 55 60

Arg Ser Leu Pro Glu Asn Glu Glu Tyr Glu Thr Asp Gln Ile Leu Pro
65 70 75 80

Asp Leu Ala Trp Met Arg Gln Ile Glu Gly Ala Val Leu Lys Pro Thr
85 90 95

Leu Ser Leu Pro Ile Gly Asp Gln Glu Tyr Phe Pro Lys Tyr Tyr Pro
100 105 110

Thr His Arg Pro Ser Lys Glu Lys Pro Asn Ala Tyr Pro Pro Asp Ile
115 120 125

Ala Leu Leu Lys Gln Met Ile Tyr Leu Phe Leu Gln Val Pro Glu Ala
130 135 140

Asn Glu Gly Leu Lys Asp Glu Val Thr Leu Leu Thr Gln Asn Ile Arg
145 150 155 160

Asp Lys Ala Tyr Gly Ser Gly Thr Tyr Met Gly Gln Ala Asn Arg Leu
165 170 175

Val Ala Met Lys Glu Val Ala Thr Gly Arg Asn Pro Asn Lys Asp Pro
180 185 190

Leu Lys Leu Gly Tyr Thr Phe Glu Ser Ile Ala Gln Leu Leu Asp Ile
195 200 205

Thr Leu Pro Val Gly Pro Pro Gly Glu Asp Asp Lys Pro Trp Val Pro
210 215 220

Leu Thr Arg Val Pro Ser Arg Met Leu Val Leu Thr Gly Asp Val Asp
225 230 235 240

Gly Asp Phe Glu Val Glu Asp Tyr Leu Pro Lys Ile Asn Leu Lys Ser
245 250 255

Ser Ser Gly Leu Pro Tyr Val Gly Arg Thr Lys Gly Glu Thr Ile Gly
260 265 270

Glu Met Ile Ala Ile Ser Asn Gln Phe Leu Arg Glu Leu Ser Thr Leu
275 280 285

Leu Lys Gln Gly Ala Gly Thr Lys Gly Ser Asn Lys Lys Lys Leu Leu

290 295 300

Ser Met Leu Ser Asp Tyr Trp Tyr Leu Ser Cys Gly Leu Leu Phe Pro
305 310 315 320

Lys Ala Glu Arg Tyr Asp Lys Ser Thr Trp Leu Thr Lys Thr Arg Asn
325 330 335

Ile Trp Ser Ala Pro Ser Pro Thr His Leu Met Ile Ser Met Ile Thr
340 345 350

Trp Pro Val Met Ser Asn Ser Pro Asn Asn Val Leu Asn Ile Glu Gly
355 360 365

Cys Pro Ser Leu Tyr Lys Phe Asn Pro Phe Arg Gly Gly Leu Asn Arg
370 375 380

Ile Val Glu Trp Ile Leu Ala Pro Glu Glu Pro Lys Ala Leu Val Tyr
385 390 395 400

Ala Asp Asn Ile Tyr Ile Val His Ser Asn Thr Trp Tyr Ser Ile Asp
405 410 415

Leu Glu Lys Gly Glu Ala Asn Cys Thr Arg Gln His Met Gln Ala Ala
420 425 430

Met Tyr Tyr Ile Leu Thr Arg Gly Trp Ser Asp Asn Gly Asp Pro Met
435 440 445

Phe Asn Gln Thr Trp Ala Thr Phe Ala Met Asn Ile Ala Pro Ala Leu
450 455 460

Val Val Asp Ser Ser Cys Leu Ile Met Asn Leu Gln Ile Lys Thr Tyr
465 470 475 480

Gly Gln Gly Ser Gly Asn Ala Ala Thr Phe Ile Asn Asn His Leu Leu
485 490 495

Ser Thr Leu Val Leu Asp Gln Trp Asn Leu Met Arg Gln Pro Arg Pro
500 505 510

Asp Ser Glu Glu Phe Lys Ser Ile Glu Asp Lys Leu Gly Ile Asn Phe
515 520 525

Lys Ile Glu Arg Ser Ile Asp Asp Ile Arg Gly Lys Leu Arg Gln Leu
530 535 540

Val Leu Leu Ala Gln Pro Gly Tyr Leu Ser Gly Gly Val Glu Pro Glu
545 550 555 560

Gln Ser Ser Pro Thr Val Glu Leu Asp Leu Leu Gly Trp Ser Ala Thr

565 570 575

Tyr Ser Lys Asp Leu Gly Ile Tyr Val Pro Val Leu Asp Lys Glu Arg
580 585 590

Leu Phe Cys Ser Ala Ala Tyr Pro Lys Gly Val Glu Asn Lys Ser Leu
595 600 605

Lys Ser Lys Val Gly Ile Glu Gln Ala Tyr Lys Val Val Arg Tyr Glu
610 615 620

Ala Leu Arg Leu Val Gly Gly Trp Asn Tyr Pro Leu Leu Asn Lys Ala
625 630 635 640

Cys Lys Asn Asn Ala Gly Ala Ala Arg Arg His Leu Glu Ala Lys Gly
645 650 655

Phe Pro Leu Asp Glu Phe Leu Ala Glu Trp Ser Glu Leu Ser Glu Phe
660 665 670

Gly Glu Ala Phe Glu Gly Phe Asn Ile Lys Leu Thr Val Thr Ser Glu
675 680 685

Ser Leu Ala Glu Leu Asn Lys Pro Val Pro Pro Lys Pro Pro Asn Val
690 695 700

Asn Arg Pro Val Asn Thr Gly Gly Leu Lys Ala Val Ser Asn Ala Leu
705 710 715 720

Lys Thr Gly Arg Tyr Arg Asn Glu Ala Gly Leu Ser Gly Leu Val Leu
725 730 735

Leu Ala Thr Ala Arg Ser Arg Leu Gln Asp Ala Val Lys Ala Lys Ala
740 745 750

Glu Ala Glu Lys Leu His Lys Ser Lys Pro Asp Asp Pro Asp Ala Asp
755 760 765

Trp Phe Glu Arg Ser Glu Thr Leu Ser Asp Leu Leu Glu Lys Ala Asp
770 775 780

Ile Ala Ser Lys Val Ala His Ser Ala Leu Val Glu Thr Ser Asp Ala
785 790 795 800

Leu Glu Ala Val Gln Ser Thr Ser Val Tyr Thr Pro Lys Tyr Pro Glu
805 810 815

Val Lys Asn Pro Gln Thr Ala Ser Asn Pro Val Val Gly Leu His Leu
820 825 830

Pro Ala Lys Arg Ala Thr Gly Val Gln Ala Ala Leu Leu Gly Ala Gly

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        835                 840                 845

Thr Ser Arg Pro Met Gly Met Glu Ala Pro Thr Arg Ser Lys Asn Ala
    850                 855                 860

Val Lys Met Ala Lys Arg Arg Gln Arg Gln Lys Glu Ser Arg
865                 870                 875
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(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3261 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 97..531

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

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GGATACGATC GGTCTGACCC CGGGGGAGTC ACCCGGGGAC AGGCCGTCAA GGCCTTGTTC      60

CAGGATGGGA CTCCTCCTTC TACAACGCTA TCATTG ATG GTT AGT AGA GAT CAG     114
                                        Met Val Ser Arg Asp Gln
                                                880

ACA AAC GAT CGC AGC GAT GAC AAA CCT GCA AGA TCA AAC CCA ACA GAT     162
Thr Asn Asp Arg Ser Asp Asp Lys Pro Ala Arg Ser Asn Pro Thr Asp
885                 890                 895                 900

TGT TCC GTT CAT ACG GAG CCT TCT GAT GCC AAC AAC CGG ACC GGC GTC     210
Cys Ser Val His Thr Glu Pro Ser Asp Ala Asn Asn Arg Thr Gly Val
                905                 910                 915

CAT TCC GGA CGA CAC CCT GGA GAA GCA CAC TCT CAG GTC AGA GAC CTC     258
His Ser Gly Arg His Pro Gly Glu Ala His Ser Gln Val Arg Asp Leu
            920                 925                 930

GAC CTA CAA TTT GAC TGT GGG GGA CAC AGG GTC AGG GCT AAT TGT CTT     306
Asp Leu Gln Phe Asp Cys Gly Gly His Arg Val Arg Ala Asn Cys Leu
        935                 940                 945

TTT CCC TGG ATT CCC TGG CTC AAT TGT GGG TGC TCA CTA CAC ACT GCA     354
Phe Pro Trp Ile Pro Trp Leu Asn Cys Gly Cys Ser Leu His Thr Ala
    950                 955                 960
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GGG CAA TGG GAA CTA CAA GTT CGA TCA GAT GCT CCT GAC TGC CCA GAA 402
Gly Gln Trp Glu Leu Gln Val Arg Ser Asp Ala Pro Asp Cys Pro Glu
965 970 975 980

CCT ACC GGC CAG TTA CAA CTA CTG CAG GCT AGT GAG TCG GAG TCT CAC 450
Pro Thr Gly Gln Leu Gln Leu Leu Gln Ala Ser Glu Ser Glu Ser His
985 990 995

AGT GAG GTC AAG CAC ACT TCC TGG TGG CGT TTA TGC ACT AAA CGG CAC 498
Ser Glu Val Lys His Thr Ser Trp Trp Arg Leu Cys Thr Lys Arg His
1000 1005 1010

CAT AAA CGC CGT GAC CTT CCA AGG AAG CCT GAG TGAACTGACA GATGTTAGCT 551
His Lys Arg Arg Asp Leu Pro Arg Lys Pro Glu
1015 1020

ACAATGGGTT GATGTCTGCA ACAGCCAACA TCAACGACAA AATTGGGAAC GTCCTAGTAG 611

GGGAAGGGGT CACCGTCCTC AGCTTACCCA CATCATATGA TCTTGGGTAT GTGAGGCTTG 671

GTGACCCCAT TCCCGCAATA GGGCTTGACC CAAAAATGGT AGCCACATGT GACAGCAGTG 731

ACAGGCCCAG AGTCTACACC ATAACTGCAG CCGATGATTA CCAATTCTCA TCACAGTACC 791

AACCAGGTGG GGTAACAATC ACACTGTTCT CAGCCAACAT TGATGCCATC ACAAGCCTCA 851

GCGTTGGGGG AGAGCTCGTG TTTCAAACAA GCGTCCACGG CCTTGTACTG GGCGCCACCA 911

TCTACCTCAT AGGCTTTGAT GGGACAACGG TAATCACCAG GGCTGTGGCC GCAAACAATG 971

GGCTGACGAC CGGCACCGAC AACCTTATGC CATTCAATCT TGTGATTCCA ACAAACGAGA 1031

TAACCCAGCC AATCACATCC ATCAAACTGG AGATAGTGAC CTCCAAAAGT GGTGGTCAGG 1091

CAGGGGATCA GATGTCATGG TCGGCAAGAG GGAGCCTAGC AGTGACGATC CATGGTGGCA 1151

ACTATCCAGG GGCCCTCCGT CCCGTCACGC TAGTGGCCTA CGAAAGAGTG GCAACAGGAT 1211

CCGTCGTTAC GGTCGCTGGG GTGAGCAACT TCGAGCTGAT CCCAAATCCT GAACTAGCAA 1271

AGAACCTGGT TACAGAATAC GGCCGATTTG ACCCAGGAGC CATGAACTAC ACAAAATTGA 1331

TACTGAGTGA GAGGGACCGT CTTGGCATCA AGACCGTCTG GCCAACAAGG GAGTACACTG 1391

ACTTTCGTGA ATACTTCATG GAGGTGGCCG ACCTCAACTC TCCCCTGAAG ATTGCAGGAG 1451

CATTCGGCTT CAAAGACATA ATCCGGGCCA TAAGGAGGAT AGCTGTGCCG GTGGTCTCCA 1511

CATTGTTCCC ACCTGCCGCT CCCCTAGCCC ATGCAATTGG GGAAGGTGTA GACTACCTGC 1571

TGGGCGATGA GGCACAGGCT GCTTCAGGAA CTGCTCGAGC CGCGTCAGGA AAAGCAAGAG 1631

CTGCCTCAGG CCGCATAAGG CAGCTGACTC TCGCCGCCGA CAAGGGGTAC GAGGTAGTCG 1691

CGAATCTATT CCAGGTGCCC CAGAATCCCG TAGTCGACGG GATTCTTGCT TCACCTGGGG 1751

TACTCCGCGG TGCACACAAC CTCGACTGCG TGTTAAGAGA GGGTGCCACG CTATTCCCTG 1811

TGGTTATTAC GACAGTGGAA GACGCCATGA CACCCAAAGC ATTGAACAGC AAAATGTTTG 1871

CTGTCATTGA AGGCGTGCGA GAAGACCTCC AACCTCCATC TCAAAGAGGA TCCTTCATAC 1931

GAACTCTCTC TGGACACAGA GTCTATGGAT ATGCTCCAGA TGGGGTACTT CCACTGGAGA 1991

CTGGGAGAGA CTACACCGTT GTCCCAATAG ATGATGTCTG GGACGACAGC ATTATGCTGT 2051

CCAAAGATCC CATACCTCCT ATTGTGGGAA ACAGTGGAAA TCTAGCCATA GCTTACATGG 2111

ATGTGTTTCG ACCCAAAGTC CCAATCCATG TGGCTATGAC GGGAGCCCTC AATGCTTGTG 2171

GCGAGATTGA GAAAGTAAGC TTTAGAAGCA CCAAGCTCGC CACTGCACAC CGACTTGGCC 2231

TTAGGTTGGC TGGTCCCGGA GCATTCGATG TAAACACCGG GCCCAACTGG GCAACGTTCA 2291

TCAAACGTTT CCCTCACAAT CCACGCGACT GGGACAGGCT CCCCTACCTC AACCTACCAT 2351

ACCTTCCACC CAATGCAGGA CGCCAGTACC ACCTTGCCAT GGCTGCATCA GAGTTCAAAG 2411

AGACCCCCGA ACTCGAGAGT GCCGTCAGAG CAATGGAAGC AGCAGCCAAC GTGGACCCAC 2471

TATTCCAATC TGCACTCAGT GTGTTCATGT GGCTGGAAGA GAATGGGATT GTGACTGACA 2531

TGGCCAACTT CGCACTCAGC GACCCGAACG CCCATCGGAT GCGAAATTTT CTTGCAAACG 2591

CACCACAAGC AGGCAGCAAG TCGCAAAGGG CCAAGTACGG GACAGCAGGC TACGGAGTGG 2651

AGGCTCGGGG CCCCACACCA GAGGAAGCAC AGAGGGAAAA AGACACACGG ATCTCAAAGA 2711

AGATGGAGAC CATGGGCATC TACTTTGCAA CACCAGAATG GGTAGCACTC AATGGGCACC 2771

GAGGGCCAAG CCCCGGCCAG CTAAAGTACT GGCAGAACAC ACGAGAAATA CCGGACCCAA 2831

ACGAGGACTA TCTAGACTAC GTGCATGCAG AGAAGAGCCG GTTGGCATCA GAAGAACAAA 2891

TCCTAAGGGC AGCTACGTCG ATCTACGGGG CTCCAGGACA GGCAGAGCCA CCCCAAGCTT 2951

TCATAGACGA AGTTGCCAAA GTCTATGAAA TCAACCATGG ACGTGGCCCA AACCAAGAAC 3011

AGATGAAAGA TCTGCTCTTG ACTGCGATGG AGATGAAGCA TCGCAATCCC AGGCGGGCTC 3071

TACCAAAGCC CAAGCCAAAA CCCAATGCTC CAACACAGAG ACCCCCTGGT CGGCTGGGCC 3131

GCTGGATCAG GACCGTCTCT GATGAGGACC TTGAGTGAGG CTCCTGGGAG TCTCCCGACA 3191

CCACCCGCGC AGGTGTGGAC ACCAATTCGG CCTTACAACA TCCCAAATTG GATCCGTTCG 3251

CGGGTCCCCT 3261

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 145 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

Met Val Ser Arg Asp Gln Thr Asn Asp Arg Ser Asp Asp Lys Pro Ala
1 5 10 15

Arg Ser Asn Pro Thr Asp Cys Ser Val His Thr Glu Pro Ser Asp Ala
20 25 30

Asn Asn Arg Thr Gly Val His Ser Gly Arg His Pro Gly Glu Ala His
35 40 45

Ser Gln Val Arg Asp Leu Asp Leu Gln Phe Asp Cys Gly Gly His Arg
50 55 60

Val Arg Ala Asn Cys Leu Phe Pro Trp Ile Pro Trp Leu Asn Cys Gly
65 70 75 80

Cys Ser Leu His Thr Ala Gly Gln Trp Glu Leu Gln Val Arg Ser Asp
85 90 95

Ala Pro Asp Cys Pro Glu Pro Thr Gly Gln Leu Gln Leu Leu Gln Ala
100 105 110

Ser Glu Ser Glu Ser His Ser Glu Val Lys His Thr Ser Trp Trp Arg
115 120 125

Leu Cys Thr Lys Arg His His Lys Arg Arg Asp Leu Pro Arg Lys Pro
130 135 140

Glu
145

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 3261 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 131..3166

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

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GGATACGATC GGTCTGACCC CGGGGGAGTC ACCCGGGGAC AGGCCGTCAA GGCCTTGTTC    60

CAGGATGGGA CTCCTCCTTC TACAACGCTA TCATTGATGG TTAGTAGAGA TCAGACAAAC   120

GATCGCAGCG ATG ACA AAC CTG CAA GAT CAA ACC CAA CAG ATT GTT CCG      169
           Met Thr Asn Leu Gln Asp Gln Thr Gln Gln Ile Val Pro
                               150                 155

TTC ATA CGG AGC CTT CTG ATG CCA ACA ACC GGA CCG GCG TCC ATT CCG      217
Phe Ile Arg Ser Leu Leu Met Pro Thr Thr Gly Pro Ala Ser Ile Pro
    160                 165                 170

GAC GAC ACC CTG GAG AAG CAC ACT CTC AGG TCA GAG ACC TCG ACC TAC      265
Asp Asp Thr Leu Glu Lys His Thr Leu Arg Ser Glu Thr Ser Thr Tyr
175                 180                 185                 190

AAT TTG ACT GTG GGG GAC ACA GGG TCA GGG CTA ATT GTC TTT TTC CCT      313
Asn Leu Thr Val Gly Asp Thr Gly Ser Gly Leu Ile Val Phe Phe Pro
                195                 200                 205

GGA TTC CCT GGC TCA ATT GTG GGT GCT CAC TAC ACA CTG CAG GGC AAT      361
Gly Phe Pro Gly Ser Ile Val Gly Ala His Tyr Thr Leu Gln Gly Asn
            210                 215                 220

GGG AAC TAC AAG TTC GAT CAG ATG CTC CTG ACT GCC CAG AAC CTA CCG      409
Gly Asn Tyr Lys Phe Asp Gln Met Leu Leu Thr Ala Gln Asn Leu Pro
        225                 230                 235

GCC AGT TAC AAC TAC TGC AGG CTA GTG AGT CGG AGT CTC ACA GTG AGG      457
Ala Ser Tyr Asn Tyr Cys Arg Leu Val Ser Arg Ser Leu Thr Val Arg
    240                 245                 250

TCA AGC ACA CTT CCT GGT GGC GTT TAT GCA CTA AAC GGC ACC ATA AAC      505
Ser Ser Thr Leu Pro Gly Gly Val Tyr Ala Leu Asn Gly Thr Ile Asn
255                 260                 265                 270

GCC GTG ACC TTC CAA GGA AGC CTG AGT GAA CTG ACA GAT GTT AGC TAC      553
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Ala Val Thr Phe Gln Gly Ser Leu Ser Glu Leu Thr Asp Val Ser Tyr
275 280 285

AAT GGG TTG ATG TCT GCA ACA GCC AAC ATC AAC GAC AAA ATT GGG AAC 601
Asn Gly Leu Met Ser Ala Thr Ala Asn Ile Asn Asp Lys Ile Gly Asn
290 295 300

GTC CTA GTA GGG GAA GGG GTC ACC GTC CTC AGC TTA CCC ACA TCA TAT 649
Val Leu Val Gly Glu Gly Val Thr Val Leu Ser Leu Pro Thr Ser Tyr
305 310 315

GAT CTT GGG TAT GTG AGG CTT GGT GAC CCC ATT CCC GCA ATA GGG CTT 697
Asp Leu Gly Tyr Val Arg Leu Gly Asp Pro Ile Pro Ala Ile Gly Leu
320 325 330

GAC CCA AAA ATG GTA GCC ACA TGT GAC AGC AGT GAC AGG CCC AGA GTC 745
Asp Pro Lys Met Val Ala Thr Cys Asp Ser Ser Asp Arg Pro Arg Val
335 340 345 350

TAC ACC ATA ACT GCA GCC GAT GAT TAC CAA TTC TCA TCA CAG TAC CAA 793
Tyr Thr Ile Thr Ala Ala Asp Asp Tyr Gln Phe Ser Ser Gln Tyr Gln
355 360 365

CCA GGT GGG GTA ACA ATC ACA CTG TTC TCA GCC AAC ATT GAT GCC ATC 841
Pro Gly Gly Val Thr Ile Thr Leu Phe Ser Ala Asn Ile Asp Ala Ile
370 375 380

ACA AGC CTC AGC GTT GGG GGA GAG CTC GTG TTT CAA ACA AGC GTC CAC 889
Thr Ser Leu Ser Val Gly Gly Glu Leu Val Phe Gln Thr Ser Val His
385 390 395

GGC CTT GTA CTG GGC GCC ACC ATC TAC CTC ATA GGC TTT GAT GGG ACA 937
Gly Leu Val Leu Gly Ala Thr Ile Tyr Leu Ile Gly Phe Asp Gly Thr
400 405 410

ACG GTA ATC ACC AGG GCT GTG GCC GCA AAC AAT GGG CTG ACG ACC GGC 985
Thr Val Ile Thr Arg Ala Val Ala Ala Asn Asn Gly Leu Thr Thr Gly
415 420 425 430

ACC GAC AAC CTT ATG CCA TTC AAT CTT GTG ATT CCA ACA AAC GAG ATA 1033
Thr Asp Asn Leu Met Pro Phe Asn Leu Val Ile Pro Thr Asn Glu Ile
435 440 445

ACC CAG CCA ATC ACA TCC ATC AAA CTG GAG ATA GTG ACC TCC AAA AGT 1081
Thr Gln Pro Ile Thr Ser Ile Lys Leu Glu Ile Val Thr Ser Lys Ser
450 455 460

GGT GGT CAG GCA GGG GAT CAG ATG TCA TGG TCG GCA AGA GGG AGC CTA 1129
Gly Gly Gln Ala Gly Asp Gln Met Ser Trp Ser Ala Arg Gly Ser Leu
465 470 475

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GCA GTG ACG ATC CAT GGT GGC AAC TAT CCA GGG GCC CTC CGT CCC GTC     1177
Ala Val Thr Ile His Gly Gly Asn Tyr Pro Gly Ala Leu Arg Pro Val
    480                 485                 490

ACG CTA GTG GCC TAC GAA AGA GTG GCA ACA GGA TCC GTC GTT ACG GTC     1225
Thr Leu Val Ala Tyr Glu Arg Val Ala Thr Gly Ser Val Val Thr Val
495                 500                 505                 510

GCT GGG GTG AGC AAC TTC GAG CTG ATC CCA AAT CCT GAA CTA GCA AAG     1273
Ala Gly Val Ser Asn Phe Glu Leu Ile Pro Asn Pro Glu Leu Ala Lys
                515                 520                 525

AAC CTG GTT ACA GAA TAC GGC CGA TTT GAC CCA GGA GCC ATG AAC TAC     1321
Asn Leu Val Thr Glu Tyr Gly Arg Phe Asp Pro Gly Ala Met Asn Tyr
            530                 535                 540

ACA AAA TTG ATA CTG AGT GAG AGG GAC CGT CTT GGC ATC AAG ACC GTC     1369
Thr Lys Leu Ile Leu Ser Glu Arg Asp Arg Leu Gly Ile Lys Thr Val
        545                 550                 555

TGG CCA ACA AGG GAG TAC ACT GAC TTT CGT GAA TAC TTC ATG GAG GTG     1417
Trp Pro Thr Arg Glu Tyr Thr Asp Phe Arg Glu Tyr Phe Met Glu Val
    560                 565                 570

GCC GAC CTC AAC TCT CCC CTG AAG ATT GCA GGA GCA TTC GGC TTC AAA     1465
Ala Asp Leu Asn Ser Pro Leu Lys Ile Ala Gly Ala Phe Gly Phe Lys
575                 580                 585                 590

GAC ATA ATC CGG GCC ATA AGG AGG ATA GCT GTG CCG GTG GTC TCC ACA     1513
Asp Ile Ile Arg Ala Ile Arg Arg Ile Ala Val Pro Val Val Ser Thr
                595                 600                 605

TTG TTC CCA CCT GCC GCT CCC CTA GCC CAT GCA ATT GGG GAA GGT GTA     1561
Leu Phe Pro Pro Ala Ala Pro Leu Ala His Ala Ile Gly Glu Gly Val
            610                 615                 620

GAC TAC CTG CTG GGC GAT GAG GCA CAG GCT GCT TCA GGA ACT GCT CGA     1609
Asp Tyr Leu Leu Gly Asp Glu Ala Gln Ala Ala Ser Gly Thr Ala Arg
        625                 630                 635

GCC GCG TCA GGA AAA GCA AGA GCT GCC TCA GGC CGC ATA AGG CAG CTG     1657
Ala Ala Ser Gly Lys Ala Arg Ala Ala Ser Gly Arg Ile Arg Gln Leu
    640                 645                 650

ACT CTC GCC GCC GAC AAG GGG TAC GAG GTA GTC GCG AAT CTA TTC CAG     1705
Thr Leu Ala Ala Asp Lys Gly Tyr Glu Val Val Ala Asn Leu Phe Gln
655                 660                 665                 670

GTG CCC CAG AAT CCC GTA GTC GAC GGG ATT CTT GCT TCA CCT GGG GTA     1753
Val Pro Gln Asn Pro Val Val Asp Gly Ile Leu Ala Ser Pro Gly Val
                675                 680                 685
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CTC CGC GGT GCA CAC AAC CTC GAC TGC GTG TTA AGA GAG GGT GCC ACG    1801
Leu Arg Gly Ala His Asn Leu Asp Cys Val Leu Arg Glu Gly Ala Thr
            690                 695                 700

CTA TTC CCT GTG GTT ATT ACG ACA GTG GAA GAC GCC ATG ACA CCC AAA    1849
Leu Phe Pro Val Val Ile Thr Thr Val Glu Asp Ala Met Thr Pro Lys
        705                 710                 715

GCA TTG AAC AGC AAA ATG TTT GCT GTC ATT GAA GGC GTG CGA GAA GAC    1897
Ala Leu Asn Ser Lys Met Phe Ala Val Ile Glu Gly Val Arg Glu Asp
    720                 725                 730

CTC CAA CCT CCA TCT CAA AGA GGA TCC TTC ATA CGA ACT CTC TCT GGA    1945
Leu Gln Pro Pro Ser Gln Arg Gly Ser Phe Ile Arg Thr Leu Ser Gly
735                 740                 745                 750

CAC AGA GTC TAT GGA TAT GCT CCA GAT GGG GTA CTT CCA CTG GAG ACT    1993
His Arg Val Tyr Gly Tyr Ala Pro Asp Gly Val Leu Pro Leu Glu Thr
                755                 760                 765

GGG AGA GAC TAC ACC GTT GTC CCA ATA GAT GAT GTC TGG GAC GAC AGC    2041
Gly Arg Asp Tyr Thr Val Val Pro Ile Asp Asp Val Trp Asp Asp Ser
            770                 775                 780

ATT ATG CTG TCC AAA GAT CCC ATA CCT CCT ATT GTG GGA AAC AGT GGA    2089
Ile Met Leu Ser Lys Asp Pro Ile Pro Pro Ile Val Gly Asn Ser Gly
        785                 790                 795

AAT CTA GCC ATA GCT TAC ATG GAT GTG TTT CGA CCC AAA GTC CCA ATC    2137
Asn Leu Ala Ile Ala Tyr Met Asp Val Phe Arg Pro Lys Val Pro Ile
    800                 805                 810

CAT GTG GCT ATG ACG GGA GCC CTC AAT GCT TGT GGC GAG ATT GAG AAA    2185
His Val Ala Met Thr Gly Ala Leu Asn Ala Cys Gly Glu Ile Glu Lys
815                 820                 825                 830

GTA AGC TTT AGA AGC ACC AAG CTC GCC ACT GCA CAC CGA CTT GGC CTT    2233
Val Ser Phe Arg Ser Thr Lys Leu Ala Thr Ala His Arg Leu Gly Leu
                835                 840                 845

AGG TTG GCT GGT CCC GGA GCA TTC GAT GTA AAC ACC GGG CCC AAC TGG    2281
Arg Leu Ala Gly Pro Gly Ala Phe Asp Val Asn Thr Gly Pro Asn Trp
            850                 855                 860

GCA ACG TTC ATC AAA CGT TTC CCT CAC AAT CCA CGC GAC TGG GAC AGG    2329
Ala Thr Phe Ile Lys Arg Phe Pro His Asn Pro Arg Asp Trp Asp Arg
        865                 870                 875

CTC CCC TAC CTC AAC CTA CCA TAC CTT CCA CCC AAT GCA GGA CGC CAG    2377
Leu Pro Tyr Leu Asn Leu Pro Tyr Leu Pro Pro Asn Ala Gly Arg Gln
    880                 885                 890
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TAC CAC CTT GCC ATG GCT GCA TCA GAG TTC AAA GAG ACC CCC GAA CTC 2425
Tyr His Leu Ala Met Ala Ala Ser Glu Phe Lys Glu Thr Pro Glu Leu
895 900 905 910

GAG AGT GCC GTC AGA GCA ATG GAA GCA GCA GCC AAC GTG GAC CCA CTA 2473
Glu Ser Ala Val Arg Ala Met Glu Ala Ala Ala Asn Val Asp Pro Leu
915 920 925

TTC CAA TCT GCA CTC AGT GTG TTC ATG TGG CTG GAA GAG AAT GGG ATT 2521
Phe Gln Ser Ala Leu Ser Val Phe Met Trp Leu Glu Glu Asn Gly Ile
930 935 940

GTG ACT GAC ATG GCC AAC TTC GCA CTC AGC GAC CCG AAC GCC CAT CGG 2569
Val Thr Asp Met Ala Asn Phe Ala Leu Ser Asp Pro Asn Ala His Arg
945 950 955

ATG CGA AAT TTT CTT GCA AAC GCA CCA CAA GCA GGC AGC AAG TCG CAA 2617
Met Arg Asn Phe Leu Ala Asn Ala Pro Gln Ala Gly Ser Lys Ser Gln
960 965 970

AGG GCC AAG TAC GGG ACA GCA GGC TAC GGA GTG GAG GCT CGG GGC CCC 2665
Arg Ala Lys Tyr Gly Thr Ala Gly Tyr Gly Val Glu Ala Arg Gly Pro
975 980 985 990

ACA CCA GAG GAA GCA CAG AGG GAA AAA GAC ACA CGG ATC TCA AAG AAG 2713
Thr Pro Glu Glu Ala Gln Arg Glu Lys Asp Thr Arg Ile Ser Lys Lys
995 1000 1005

ATG GAG ACC ATG GGC ATC TAC TTT GCA ACA CCA GAA TGG GTA GCA CTC 2761
Met Glu Thr Met Gly Ile Tyr Phe Ala Thr Pro Glu Trp Val Ala Leu
1010 1015 1020

AAT GGG CAC CGA GGG CCA AGC CCC GGC CAG CTA AAG TAC TGG CAG AAC 2809
Asn Gly His Arg Gly Pro Ser Pro Gly Gln Leu Lys Tyr Trp Gln Asn
1025 1030 1035

ACA CGA GAA ATA CCG GAC CCA AAC GAG GAC TAT CTA GAC TAC GTG CAT 2857
Thr Arg Glu Ile Pro Asp Pro Asn Glu Asp Tyr Leu Asp Tyr Val His
1040 1045 1050

GCA GAG AAG AGC CGG TTG GCA TCA GAA GAA CAA ATC CTA AGG GCA GCT 2905
Ala Glu Lys Ser Arg Leu Ala Ser Glu Glu Gln Ile Leu Arg Ala Ala
1055 1060 1065 1070

ACG TCG ATC TAC GGG GCT CCA GGA CAG GCA GAG CCA CCC CAA GCT TTC 2953
Thr Ser Ile Tyr Gly Ala Pro Gly Gln Ala Glu Pro Pro Gln Ala Phe
1075 1080 1085

ATA GAC GAA GTT GCC AAA GTC TAT GAA ATC AAC CAT GGA CGT GGC CCA 3001
Ile Asp Glu Val Ala Lys Val Tyr Glu Ile Asn His Gly Arg Gly Pro
1090 1095 1100

```
AAC CAA GAA CAG ATG AAA GAT CTG CTC TTG ACT GCG ATG GAG ATG AAG      3049
Asn Gln Glu Gln Met Lys Asp Leu Leu Leu Thr Ala Met Glu Met Lys
        1105                1110                1115

CAT CGC AAT CCC AGG CGG GCT CTA CCA AAG CCC AAG CCA AAA CCC AAT      3097
His Arg Asn Pro Arg Arg Ala Leu Pro Lys Pro Lys Pro Lys Pro Asn
    1120                1125                1130

GCT CCA ACA CAG AGA CCC CCT GGT CGG CTG GGC CGC TGG ATC AGG ACC      3145
Ala Pro Thr Gln Arg Pro Pro Gly Arg Leu Gly Arg Trp Ile Arg Thr
1135                1140                1145                1150

GTC TCT GAT GAG GAC CTT GAG TGAGGCTCCT GGGAGTCTCC CGACACCACC         3196
Val Ser Asp Glu Asp Leu Glu
                1155

CGCGCAGGTG TGGACACCAA TTCGGCCTTA CAACATCCCA AATTGGATCC GTTCGCGGGT    3256

CCCCT                                                                3261
```

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1012 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```
Met Thr Asn Leu Gln Asp Gln Thr Gln Gln Ile Val Pro Phe Ile Arg
  1               5                  10                  15

Ser Leu Leu Met Pro Thr Thr Gly Pro Ala Ser Ile Pro Asp Asp Thr
             20                  25                  30

Leu Glu Lys His Thr Leu Arg Ser Glu Thr Ser Thr Tyr Asn Leu Thr
         35                  40                  45

Val Gly Asp Thr Gly Ser Gly Leu Ile Val Phe Phe Pro Gly Phe Pro
     50                  55                  60

Gly Ser Ile Val Gly Ala His Tyr Thr Leu Gln Gly Asn Gly Asn Tyr
 65                  70                  75                  80

Lys Phe Asp Gln Met Leu Leu Thr Ala Gln Asn Leu Pro Ala Ser Tyr
                 85                  90                  95

Asn Tyr Cys Arg Leu Val Ser Arg Ser Leu Thr Val Arg Ser Ser Thr
            100                 105                 110
```

Leu Pro Gly Gly Val Tyr Ala Leu Asn Gly Thr Ile Asn Ala Val Thr
115 120 125

Phe Gln Gly Ser Leu Ser Glu Leu Thr Asp Val Ser Tyr Asn Gly Leu
130 135 140

Met Ser Ala Thr Ala Asn Ile Asn Asp Lys Ile Gly Asn Val Leu Val
145 150 155 160

Gly Glu Gly Val Thr Val Leu Ser Leu Pro Thr Ser Tyr Asp Leu Gly
165 170 175

Tyr Val Arg Leu Gly Asp Pro Ile Pro Ala Ile Gly Leu Asp Pro Lys
180 185 190

Met Val Ala Thr Cys Asp Ser Ser Asp Arg Pro Arg Val Tyr Thr Ile
195 200 205

Thr Ala Ala Asp Asp Tyr Gln Phe Ser Ser Gln Tyr Gln Pro Gly Gly
210 215 220

Val Thr Ile Thr Leu Phe Ser Ala Asn Ile Asp Ala Ile Thr Ser Leu
225 230 235 240

Ser Val Gly Gly Glu Leu Val Phe Gln Thr Ser Val His Gly Leu Val
245 250 255

Leu Gly Ala Thr Ile Tyr Leu Ile Gly Phe Asp Gly Thr Thr Val Ile
260 265 270

Thr Arg Ala Val Ala Ala Asn Asn Gly Leu Thr Thr Gly Thr Asp Asn
275 280 285

Leu Met Pro Phe Asn Leu Val Ile Pro Thr Asn Glu Ile Thr Gln Pro
290 295 300

Ile Thr Ser Ile Lys Leu Glu Ile Val Thr Ser Lys Ser Gly Gly Gln
305 310 315 320

Ala Gly Asp Gln Met Ser Trp Ser Ala Arg Gly Ser Leu Ala Val Thr
325 330 335

Ile His Gly Gly Asn Tyr Pro Gly Ala Leu Arg Pro Val Thr Leu Val
340 345 350

Ala Tyr Glu Arg Val Ala Thr Gly Ser Val Val Thr Val Ala Gly Val
355 360 365

Ser Asn Phe Glu Leu Ile Pro Asn Pro Glu Leu Ala Lys Asn Leu Val
370 375 380

Thr Glu Tyr Gly Arg Phe Asp Pro Gly Ala Met Asn Tyr Thr Lys Leu

385 390 395 400

Ile Leu Ser Glu Arg Asp Arg Leu Gly Ile Lys Thr Val Trp Pro Thr
405 410 415

Arg Glu Tyr Thr Asp Phe Arg Glu Tyr Phe Met Glu Val Ala Asp Leu
420 425 430

Asn Ser Pro Leu Lys Ile Ala Gly Ala Phe Gly Phe Lys Asp Ile Ile
435 440 445

Arg Ala Ile Arg Arg Ile Ala Val Pro Val Val Ser Thr Leu Phe Pro
450 455 460

Pro Ala Ala Pro Leu Ala His Ala Ile Gly Glu Gly Val Asp Tyr Leu
465 470 475 480

Leu Gly Asp Glu Ala Gln Ala Ala Ser Gly Thr Ala Arg Ala Ala Ser
485 490 495

Gly Lys Ala Arg Ala Ala Ser Gly Arg Ile Arg Gln Leu Thr Leu Ala
500 505 510

Ala Asp Lys Gly Tyr Glu Val Val Ala Asn Leu Phe Gln Val Pro Gln
515 520 525

Asn Pro Val Val Asp Gly Ile Leu Ala Ser Pro Gly Val Leu Arg Gly
530 535 540

Ala His Asn Leu Asp Cys Val Leu Arg Glu Gly Ala Thr Leu Phe Pro
545 550 555 560

Val Val Ile Thr Thr Val Glu Asp Ala Met Thr Pro Lys Ala Leu Asn
565 570 575

Ser Lys Met Phe Ala Val Ile Glu Gly Val Arg Glu Asp Leu Gln Pro
580 585 590

Pro Ser Gln Arg Gly Ser Phe Ile Arg Thr Leu Ser Gly His Arg Val
595 600 605

Tyr Gly Tyr Ala Pro Asp Gly Val Leu Pro Leu Glu Thr Gly Arg Asp
610 615 620

Tyr Thr Val Val Pro Ile Asp Asp Val Trp Asp Asp Ser Ile Met Leu
625 630 635 640

Ser Lys Asp Pro Ile Pro Pro Ile Val Gly Asn Ser Gly Asn Leu Ala
645 650 655

Ile Ala Tyr Met Asp Val Phe Arg Pro Lys Val Pro Ile His Val Ala
660 665 670

Met Thr Gly Ala Leu Asn Ala Cys Gly Glu Ile Glu Lys Val Ser Phe
        675   680   685

Arg Ser Thr Lys Leu Ala Thr Ala His Arg Leu Gly Leu Arg Leu Ala
    690   695   700

Gly Pro Gly Ala Phe Asp Val Asn Thr Gly Pro Asn Trp Ala Thr Phe
705   710   715   720

Ile Lys Arg Phe Pro His Asn Pro Arg Asp Trp Asp Arg Leu Pro Tyr
                725   730   735

Leu Asn Leu Pro Tyr Leu Pro Pro Asn Ala Gly Arg Gln Tyr His Leu
            740   745   750

Ala Met Ala Ala Ser Glu Phe Lys Glu Thr Pro Glu Leu Glu Ser Ala
        755   760   765

Val Arg Ala Met Glu Ala Ala Ala Asn Val Asp Pro Leu Phe Gln Ser
    770   775   780

Ala Leu Ser Val Phe Met Trp Leu Glu Glu Asn Gly Ile Val Thr Asp
785   790   795   800

Met Ala Asn Phe Ala Leu Ser Asp Pro Asn Ala His Arg Met Arg Asn
                805   810   815

Phe Leu Ala Asn Ala Pro Gln Ala Gly Ser Lys Ser Gln Arg Ala Lys
            820   825   830

Tyr Gly Thr Ala Gly Tyr Gly Val Glu Ala Arg Gly Pro Thr Pro Glu
        835   840   845

Glu Ala Gln Arg Glu Lys Asp Thr Arg Ile Ser Lys Lys Met Glu Thr
    850   855   860

Met Gly Ile Tyr Phe Ala Thr Pro Glu Trp Val Ala Leu Asn Gly His
865   870   875   880

Arg Gly Pro Ser Pro Gly Gln Leu Lys Tyr Trp Gln Asn Thr Arg Glu
                885   890   895

Ile Pro Asp Pro Asn Glu Asp Tyr Leu Asp Tyr Val His Ala Glu Lys
            900   905   910

Ser Arg Leu Ala Ser Glu Glu Gln Ile Leu Arg Ala Ala Thr Ser Ile
        915   920   925

Tyr Gly Ala Pro Gly Gln Ala Glu Pro Pro Gln Ala Phe Ile Asp Glu
    930   935   940

Val Ala Lys Val Tyr Glu Ile Asn His Gly Arg Gly Pro Asn Gln Glu

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945                 950                 955                 960

Gln Met Lys Asp Leu Leu Leu Thr Ala Met Glu Met Lys His Arg Asn
                965                 970                 975

Pro Arg Arg Ala Leu Pro Lys Pro Lys Pro Lys Pro Asn Ala Pro Thr
            980                 985                 990

Gln Arg Pro Pro Gly Arg Leu Gly Arg Trp Ile Arg Thr Val Ser Asp
        995                 1000                1005

Glu Asp Leu Glu
    1010
```

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3264 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 97..531

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```
GGATACGATC GGTCTGACCC CGGGGGAGTC ACCCGGGGAC AGGCCATCAC TGCCTTGTTC     60

CTGGTTGGAA CTCCTCTTTC TGCTGTACTA TCGTTG ATG GTG AGT AGA GAT CAG      114
                                        Met Val Ser Arg Asp Gln
                                                1015

ACA AAC GAT CGC AGC GAT GAC AAA CCT GAT GGA TCA CAC CCA ACA GAT      162
Thr Asn Asp Arg Ser Asp Asp Lys Pro Asp Gly Ser His Pro Thr Asp
    1020                1025                1030

TGT TCC GTT CAT ACG GAG CCT TCT GAT GCC AAC GAC CGG ACC GGC GTC      210
Cys Ser Val His Thr Glu Pro Ser Asp Ala Asn Asp Arg Thr Gly Val
1035                1040                1045                1050

CAT TCC GGA CGA CAC CCT GGA GAA GCA CAC ACT CAG GTC CGA AAC CTC      258
His Ser Gly Arg His Pro Gly Glu Ala His Thr Gln Val Arg Asn Leu
                1055                1060                1065

GAC TTA CAA CTT GAC TGT AGG GGA TAC AGG GTC AGG ACT AAT TGT CTT      306
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Asp Leu Gln Leu Asp Cys Arg Gly Tyr Arg Val Arg Thr Asn Cys Leu
            1070                1075                1080

TTT CCC TGG ATT CCC TGG TTC AGT TGT AGG TGC TCA CTA CAC ACT GCA     354
Phe Pro Trp Ile Pro Trp Phe Ser Cys Arg Cys Ser Leu His Thr Ala
        1085                1090                1095

GAG CAG TGG GAA CTA CCA ATT CGA CCA GAT GCT CCT GAC AGC GCA GAA     402
Glu Gln Trp Glu Leu Pro Ile Arg Pro Asp Ala Pro Asp Ser Ala Glu
    1100                1105                1110

CCT GCC TGC CAG CTA CAA CTA CTG CAG GCT AGT GAG CAG GAG TCT AAC     450
Pro Ala Cys Gln Leu Gln Leu Leu Gln Ala Ser Glu Gln Glu Ser Asn
1115                1120                1125                1130

CGT ACG GTC AAG CAC ACT CCC TGG TGG CGT TTA TGC ACT AAA CGG AAC     498
Arg Thr Val Lys His Thr Pro Trp Trp Arg Leu Cys Thr Lys Arg Asn
                1135                1140                1145

CAT AAA CGC AGT GAC CTT CCA CGG AAG CCT GAG TGAGTTGACT GACTACAGCT    551
His Lys Arg Ser Asp Leu Pro Arg Lys Pro Glu
            1150                1155

ACAACGGGCT GATGTCAGCC ACTGCGAACA TCAACGACAA GATCGGGAAC GTTCTAGTTG    611

GAGAAGGGGT GACTGTTCTC AGTCTACCGA CTTCATATGA CCTTAGTTAT GTGAGACTCG    671

GTGACCCCAT CCCCGCAGCA GGACTCGACC CGAAGTTGAT GGCCACGTGC GACAGTAGTG    731

ACAGACCCAG AGTCTACACC ATAACAGCTG CAGATGAATA CCAATTCTCG TCACAACTCA    791

TCCCGAGTGG CGTGAAGACC ACACTGTTCT CCGCCAACAT CGATGCTCTC ACCAGCTTCA    851

GCGTTGGTGG TGAGCTTGTC TTCAGCCAAG TAACGATCCA AAGCATTGAA GTGGACGTCA    911

CCATTCACTT CATTGGGTTT GACGGGACAG ACGTAGCAGT CAAGGCAGTT GCAACAGACT    971

TTGGGCTGAC AACTGGGACA AACAACCTTG TGCCATTCAA CCTGGTGGTC CCAACAAATG   1031

AGATCACCCA GCCCATCACT TCCATGAAAC TAGAGGTTGT GACCTACAAG ATTGGCGGCA   1091

CCGCTGGTGA CCCAATATCA TGGACAGTGA GTGGTACACT AGCTGTGACG GTGCACGGAG   1151

GCAACTACCC TGGGGCTCTC CGTCCTGTCA CCCTGGTGGC CTATGAACGA GTGGCTGCAG   1211

GATCTGTTGT CACAGTTGCA GGGGTGAGCA ACTTCGAGCT AATCCCCAAC CCTGAGCTTG   1271

CAAAGAACCT AGTTACAGAG TATGGCCGCT TTGACCCCGG AGCAATGAAC TACACCAAAC   1331

TAATACTGAG TGAGAGAGAT CGTCTAGGCA TCAAGACAGT CTGGCCCACC AGGGAGTACA   1391

CCGATTTCAG GGAGTACTTC ATGGAGGTTG CAGATCTCAA CTCACCCCTA AAGATTGCAG   1451
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GAGCATTTGG CTTTAAGGAC ATAATCCGAG CCATTCGGAA GATTGCGGTG CCAGTGGTAT 1511

CCACACTCTT CCCTCCAGCT GCACCCCTAG CACATGCAAT CGGAGAAGGT GTAGACTACC 1571

TCCTGGGCGA CGAGGCCCAA GCAGCCTCAG GGACAGCTCG AGCCGCGTCA GGAAAAGCTA 1631

GAGCTGCCTC AGGACGAATA AGGCAGCTAA CTCTCGCAGC TGACAAGGGG TGCGAGGTAG 1691

TCGCCAACAT GTTCCAGGTG CCCCAGAATC CCATTGTTGA TGGCATTCTG GCATCCCCAG 1751

GAATCCTGCG TGGCGCACAC AACCTCGACT GCGTGCTATG GGAGGGAGCC ACTCTTTTCC 1811

CTGTTGTCAT TACGACACTC GAGGATGAGC TGACCCCCAA GGCACTGAAC AGCAAAATGT 1871

TTGCTGTCAT TGAAGGTGTG CGAGAGGACC TCCAGCCTCC ATCCCAACGG GGATCCTTCA 1931

TTCGAACTCT CTCTGGCCAT AGAGTCTATG GCTATGCCCC AGACGGAGTA CTGCCTCTGG 1991

AGACCGGGAG AGACTACACC GTTGTCCCAA TTGATGATGT GTGGGACGAT AGCATAATGC 2051

TGTCGCAGGA CCCCATACCT CCAATCATAG GGAACAGCGG CAACCTAGCC ATAGCATACA 2111

TGGATGTCTT CAGGCCCAAG GTCCCCATCC ACGTGGCTAT GACAGGGGCC CTCAATGCCC 2171

GCGGTGAGAT CGAGAGTGTT ACGTTCCGCA GCACCAAACT CGCCACAGCC CACCGACTTG 2231

GCATGAAGTT AGCTGGTCCT GGAGCCTATG ACATTAATAC AGGACCTAAC TGGGCAACGT 2291

TCGTCAAACG TTTCCCTCAC AATCCCCGAG ACTGGGACAG GTTGCCCTAC CTCAACCTTC 2351

CTTATCTCCC ACCAACAGCA GGACGTCAGT TCCATCTAGC CCTGGCTGCC TCCGAGTTCA 2411

AAGAGACCCC AGAACTCGAA GACGCTGTGC GCGCAATGGA TGCCGCTGCA AATGCCGACC 2471

CATTGTTCCG CTCAGCTCTC CAGGTCTTCA TGTGGTTGGA AGAAAACGGG ATTGTGACCG 2531

ACATGGCTAA CTTCGCCCTC AGCGACCCAA ACGCGCATAG GATGAAAAAC TTCCTAGCAA 2591

ACGCACCCCA GGCTGGAAGC AAGTCGCAGA GGGCCAAGTA TGGCACGGCA GGCTACGGAG 2651

TGGAGGCTCG AGGCCCCACA CCAGAAGAGG CACAGAGGGA AAAAGACACA CGGATCTCCA 2711

AGAAGATGGA AACAATGGGC ATCTACTTCG CGACACCGGA ATGGGTGGCT CTCAACGGGC 2771

ACCGAGGCCC AAGCCCCGGC CAACTCAAGT ACTGGCAAAA CACAAGAGAA ATACCAGAGC 2831

CCAATGAGGA CTACCCAGAC TATGTGCACG CGGAGAAGAG CCGGTTGGCG TCAGAAGAAC 2891

AGATCCTACG GGCAGCCACG TCGATCTACG GGGCTCCAGG ACAGGCTGAA CCACCCCAGG 2951

CCTTCATAGA CGAGGTCGCC AGGGTCTATG AAATCAACCA TGGGCGTGGT CCAAACCAGG 3011

AGCAGATGAA GGACCTGCTC CTGACTGCGA TGGAGATGAA GCATCGCAAT CCCAGGCGGG 3071

CTCCACCAAA GCCAAAGCCA AAACCCAATG CTCCATCACA GAGACCCCCT GGACGGCTGG 3131

GCCGCTGGAT CAGGACGGTC TCCGACGAGG ACTTGGAGTG AGGCTCCTGG GAGTCTCCCG 3191

ACACTACCCG CGCAGGTGTG GACACCAATT CGGCCTTCTA CCATCCCAAA TTGGATCCGT 3251

TCGCGGGTCC CCT 3264

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 145 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

Met Val Ser Arg Asp Gln Thr Asn Asp Arg Ser Asp Asp Lys Pro Asp
1 5 10 15

Gly Ser His Pro Thr Asp Cys Ser Val His Thr Glu Pro Ser Asp Ala
20 25 30

Asn Asp Arg Thr Gly Val His Ser Gly Arg His Pro Gly Glu Ala His
35 40 45

Thr Gln Val Arg Asn Leu Asp Leu Gln Leu Asp Cys Arg Gly Tyr Arg
50 55 60

Val Arg Thr Asn Cys Leu Phe Pro Trp Ile Pro Trp Phe Ser Cys Arg
65 70 75 80

Cys Ser Leu His Thr Ala Glu Gln Trp Glu Leu Pro Ile Arg Pro Asp
85 90 95

Ala Pro Asp Ser Ala Glu Pro Ala Cys Gln Leu Gln Leu Leu Gln Ala
100 105 110

Ser Glu Gln Glu Ser Asn Arg Thr Val Lys His Thr Pro Trp Trp Arg
115 120 125

Leu Cys Thr Lys Arg Asn His Lys Arg Ser Asp Leu Pro Arg Lys Pro
130 135 140

Glu
145

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3264 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: circular

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 131..3169

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

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GGATACGATC GGTCTGACCC CGGGGGAGTC ACCCGGGGAC AGGCCATCAC TGCCTTGTTC    60

CTGGTTGGAA CTCCTCTTTC TGCTGTACTA TCGTTGATGG TGAGTAGAGA TCAGACAAAC   120

GATCGCAGCG ATG ACA AAC CTG ATG GAT CAC ACC CAA CAG ATT GTT CCG      169
           Met Thr Asn Leu Met Asp His Thr Gln Gln Ile Val Pro
                               150                 155

TTC ATA CGG AGC CTT CTG ATG CCA ACG ACC GGA CCG GCG TCC ATT CCG     217
Phe Ile Arg Ser Leu Leu Met Pro Thr Thr Gly Pro Ala Ser Ile Pro
    160                 165                 170

GAC GAC ACC CTG GAG AAG CAC ACA CTC AGG TCC GAA ACC TCG ACT TAC     265
Asp Asp Thr Leu Glu Lys His Thr Leu Arg Ser Glu Thr Ser Thr Tyr
175                 180                 185                 190

AAC TTG ACT GTA GGG GAT ACA GGG TCA GGA CTA ATT GTC TTT TTC CCT     313
Asn Leu Thr Val Gly Asp Thr Gly Ser Gly Leu Ile Val Phe Phe Pro
                195                 200                 205

GGA TTC CCT GGT TCA GTT GTA GGT GCT CAC TAC ACA CTG CAG AGC AGT     361
Gly Phe Pro Gly Ser Val Val Gly Ala His Tyr Thr Leu Gln Ser Ser
            210                 215                 220

GGG AAC TAC CAA TTC GAC CAG ATG CTC CTG ACA GCG CAG AAC CTG CCT     409
Gly Asn Tyr Gln Phe Asp Gln Met Leu Leu Thr Ala Gln Asn Leu Pro
        225                 230                 235

GCC AGC TAC AAC TAC TGC AGG CTA GTG AGC AGG AGT CTA ACC GTA CGG     457
Ala Ser Tyr Asn Tyr Cys Arg Leu Val Ser Arg Ser Leu Thr Val Arg
    240                 245                 250
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TCA AGC ACA CTC CCT GGT GGC GTT TAT GCA CTA AAC GGA ACC ATA AAC 505
Ser Ser Thr Leu Pro Gly Gly Val Tyr Ala Leu Asn Gly Thr Ile Asn
255 260 265 270

GCA GTG ACC TTC CAC GGA AGC CTG AGT GAG TTG ACT GAC TAC AGC TAC 553
Ala Val Thr Phe His Gly Ser Leu Ser Glu Leu Thr Asp Tyr Ser Tyr
275 280 285

AAC GGG CTG ATG TCA GCC ACT GCG AAC ATC AAC GAC AAG ATC GGG AAC 601
Asn Gly Leu Met Ser Ala Thr Ala Asn Ile Asn Asp Lys Ile Gly Asn
290 295 300

GTT CTA GTT GGA GAA GGG GTG ACT GTT CTC AGT CTA CCG ACT TCA TAT 649
Val Leu Val Gly Glu Gly Val Thr Val Leu Ser Leu Pro Thr Ser Tyr
305 310 315

GAC CTT AGT TAT GTG AGA CTC GGT GAC CCC ATC CCC GCA GCA GGA CTC 697
Asp Leu Ser Tyr Val Arg Leu Gly Asp Pro Ile Pro Ala Ala Gly Leu
320 325 330

GAC CCG AAG TTG ATG GCC ACG TGC GAC AGT AGT GAC AGA CCC AGA GTC 745
Asp Pro Lys Leu Met Ala Thr Cys Asp Ser Ser Asp Arg Pro Arg Val
335 340 345 350

TAC ACC ATA ACA GCT GCA GAT GAA TAC CAA TTC TCG TCA CAA CTC ATC 793
Tyr Thr Ile Thr Ala Ala Asp Glu Tyr Gln Phe Ser Ser Gln Leu Ile
355 360 365

CCG AGT GGC GTG AAG ACC ACA CTG TTC TCC GCC AAC ATC GAT GCT CTC 841
Pro Ser Gly Val Lys Thr Thr Leu Phe Ser Ala Asn Ile Asp Ala Leu
370 375 380

ACC AGC TTC AGC GTT GGT GGT GAG CTT GTC TTC AGC CAA GTA ACG ATC 889
Thr Ser Phe Ser Val Gly Gly Glu Leu Val Phe Ser Gln Val Thr Ile
385 390 395

CAA AGC ATT GAA GTG GAC GTC ACC ATT CAC TTC ATT GGG TTT GAC GGG 937
Gln Ser Ile Glu Val Asp Val Thr Ile His Phe Ile Gly Phe Asp Gly
400 405 410

ACA GAC GTA GCA GTC AAG GCA GTT GCA ACA GAC TTT GGG CTG ACA ACT 985
Thr Asp Val Ala Val Lys Ala Val Ala Thr Asp Phe Gly Leu Thr Thr
415 420 425 430

GGG ACA AAC AAC CTT GTG CCA TTC AAC CTG GTG GTC CCA ACA AAT GAG 1033
Gly Thr Asn Asn Leu Val Pro Phe Asn Leu Val Val Pro Thr Asn Glu
435 440 445

ATC ACC CAG CCC ATC ACT TCC ATG AAA CTA GAG GTT GTG ACC TAC AAG 1081
Ile Thr Gln Pro Ile Thr Ser Met Lys Leu Glu Val Val Thr Tyr Lys
450 455 460

```
ATT GGC GGC ACC GCT GGT GAC CCA ATA TCA TGG ACA GTG AGT GGT ACA     1129
Ile Gly Gly Thr Ala Gly Asp Pro Ile Ser Trp Thr Val Ser Gly Thr
        465                 470                 475

CTA GCT GTG ACG GTG CAC GGA GGC AAC TAC CCT GGG GCT CTC CGT CCT     1177
Leu Ala Val Thr Val His Gly Gly Asn Tyr Pro Gly Ala Leu Arg Pro
    480                 485                 490

GTC ACC CTG GTG GCC TAT GAA CGA GTG GCT GCA GGA TCT GTT GTC ACA     1225
Val Thr Leu Val Ala Tyr Glu Arg Val Ala Ala Gly Ser Val Val Thr
495                 500                 505                 510

GTT GCA GGG GTG AGC AAC TTC GAG CTA ATC CCC AAC CCT GAG CTT GCA     1273
Val Ala Gly Val Ser Asn Phe Glu Leu Ile Pro Asn Pro Glu Leu Ala
                515                 520                 525

AAG AAC CTA GTT ACA GAG TAT GGC CGC TTT GAC CCC GGA GCA ATG AAC     1321
Lys Asn Leu Val Thr Glu Tyr Gly Arg Phe Asp Pro Gly Ala Met Asn
            530                 535                 540

TAC ACC AAA CTA ATA CTG AGT GAG AGA GAT CGT CTA GGC ATC AAG ACA     1369
Tyr Thr Lys Leu Ile Leu Ser Glu Arg Asp Arg Leu Gly Ile Lys Thr
        545                 550                 555

GTC TGG CCC ACC AGG GAG TAC ACC GAT TTC AGG GAG TAC TTC ATG GAG     1417
Val Trp Pro Thr Arg Glu Tyr Thr Asp Phe Arg Glu Tyr Phe Met Glu
    560                 565                 570

GTT GCA GAT CTC AAC TCA CCC CTA AAG ATT GCA GGA GCA TTT GGC TTT     1465
Val Ala Asp Leu Asn Ser Pro Leu Lys Ile Ala Gly Ala Phe Gly Phe
575                 580                 585                 590

AAG GAC ATA ATC CGA GCC ATT CGG AAG ATT GCG GTG CCA GTG GTA TCC     1513
Lys Asp Ile Ile Arg Ala Ile Arg Lys Ile Ala Val Pro Val Val Ser
                595                 600                 605

ACA CTC TTC CCT CCA GCT GCA CCC CTA GCA CAT GCA ATC GGA GAA GGT     1561
Thr Leu Phe Pro Pro Ala Ala Pro Leu Ala His Ala Ile Gly Glu Gly
            610                 615                 620

GTA GAC TAC CTC CTG GGC GAC GAG GCC CAA GCA GCC TCA GGG ACA GCT     1609
Val Asp Tyr Leu Leu Gly Asp Glu Ala Gln Ala Ala Ser Gly Thr Ala
        625                 630                 635

CGA GCC GCG TCA GGA AAA GCT AGA GCT GCC TCA GGA CGA ATA AGG CAG     1657
Arg Ala Ala Ser Gly Lys Ala Arg Ala Ala Ser Gly Arg Ile Arg Gln
    640                 645                 650

CTA ACT CTC GCA GCT GAC AAG GGG TGC GAG GTA GTC GCC AAC ATG TTC     1705
Leu Thr Leu Ala Ala Asp Lys Gly Cys Glu Val Val Ala Asn Met Phe
655                 660                 665                 670
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CAG GTG CCC CAG AAT CCC ATT GTT GAT GGC ATT CTG GCA TCC CCA GGA      1753
Gln Val Pro Gln Asn Pro Ile Val Asp Gly Ile Leu Ala Ser Pro Gly
                675                 680                 685

ATC CTG CGT GGC GCA CAC AAC CTC GAC TGC GTG CTA TGG GAG GGA GCC      1801
Ile Leu Arg Gly Ala His Asn Leu Asp Cys Val Leu Trp Glu Gly Ala
            690                 695                 700

ACT CTT TTC CCT GTT GTC ATT ACG ACA CTC GAG GAT GAG CTG ACC CCC      1849
Thr Leu Phe Pro Val Val Ile Thr Thr Leu Glu Asp Glu Leu Thr Pro
        705                 710                 715

AAG GCA CTG AAC AGC AAA ATG TTT GCT GTC ATT GAA GGT GTG CGA GAG      1897
Lys Ala Leu Asn Ser Lys Met Phe Ala Val Ile Glu Gly Val Arg Glu
    720                 725                 730

GAC CTC CAG CCT CCA TCC CAA CGG GGA TCC TTC ATT CGA ACT CTC TCT      1945
Asp Leu Gln Pro Pro Ser Gln Arg Gly Ser Phe Ile Arg Thr Leu Ser
735                 740                 745                 750

GGC CAT AGA GTC TAT GGC TAT GCC CCA GAC GGA GTA CTG CCT CTG GAG      1993
Gly His Arg Val Tyr Gly Tyr Ala Pro Asp Gly Val Leu Pro Leu Glu
                755                 760                 765

ACC GGG AGA GAC TAC ACC GTT GTC CCA ATT GAT GAT GTG TGG GAC GAT      2041
Thr Gly Arg Asp Tyr Thr Val Val Pro Ile Asp Asp Val Trp Asp Asp
            770                 775                 780

AGC ATA ATG CTG TCG CAG GAC CCC ATA CCT CCA ATC ATA GGG AAC AGC      2089
Ser Ile Met Leu Ser Gln Asp Pro Ile Pro Pro Ile Ile Gly Asn Ser
        785                 790                 795

GGC AAC CTA GCC ATA GCA TAC ATG GAT GTC TTC AGG CCC AAG GTC CCC      2137
Gly Asn Leu Ala Ile Ala Tyr Met Asp Val Phe Arg Pro Lys Val Pro
    800                 805                 810

ATC CAC GTG GCT ATG ACA GGG GCC CTC AAT GCC CGC GGT GAG ATC GAG      2185
Ile His Val Ala Met Thr Gly Ala Leu Asn Ala Arg Gly Glu Ile Glu
815                 820                 825                 830

AGT GTT ACG TTC CGC AGC ACC AAA CTC GCC ACA GCC CAC CGA CTT GGC      2233
Ser Val Thr Phe Arg Ser Thr Lys Leu Ala Thr Ala His Arg Leu Gly
                835                 840                 845

ATG AAG TTA GCT GGT CCT GGA GCC TAT GAC ATT AAT ACA GGA CCT AAC      2281
Met Lys Leu Ala Gly Pro Gly Ala Tyr Asp Ile Asn Thr Gly Pro Asn
            850                 855                 860

TGG GCA ACG TTC GTC AAA CGT TTC CCT CAC AAT CCC CGA GAC TGG GAC      2329
Trp Ala Thr Phe Val Lys Arg Phe Pro His Asn Pro Arg Asp Trp Asp
        865                 870                 875
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AGG TTG CCC TAC CTC AAC CTT CCT TAT CTC CCA CCA ACA GCA GGA CGT      2377
Arg Leu Pro Tyr Leu Asn Leu Pro Tyr Leu Pro Pro Thr Ala Gly Arg
    880                 885                 890

CAG TTC CAT CTA GCC CTG GCT GCC TCC GAG TTC AAA GAG ACC CCA GAA      2425
Gln Phe His Leu Ala Leu Ala Ala Ser Glu Phe Lys Glu Thr Pro Glu
895                 900                 905                 910

CTC GAA GAC GCT GTG CGC GCA ATG GAT GCC GCT GCA AAT GCC GAC CCA      2473
Leu Glu Asp Ala Val Arg Ala Met Asp Ala Ala Ala Asn Ala Asp Pro
                915                 920                 925

TTG TTC CGC TCA GCT CTC CAG GTC TTC ATG TGG TTG GAA GAA AAC GGG      2521
Leu Phe Arg Ser Ala Leu Gln Val Phe Met Trp Leu Glu Glu Asn Gly
            930                 935                 940

ATT GTG ACC GAC ATG GCT AAC TTC GCC CTC AGC GAC CCA AAC GCG CAT      2569
Ile Val Thr Asp Met Ala Asn Phe Ala Leu Ser Asp Pro Asn Ala His
        945                 950                 955

AGG ATG AAA AAC TTC CTA GCA AAC GCA CCC CAG GCT GGA AGC AAG TCG      2617
Arg Met Lys Asn Phe Leu Ala Asn Ala Pro Gln Ala Gly Ser Lys Ser
    960                 965                 970

CAG AGG GCC AAG TAT GGC ACG GCA GGC TAC GGA GTG GAG GCT CGA GGC      2665
Gln Arg Ala Lys Tyr Gly Thr Ala Gly Tyr Gly Val Glu Ala Arg Gly
975                 980                 985                 990

CCC ACA CCA GAA GAG GCA CAG AGG GAA AAA GAC ACA CGG ATC TCC AAG      2713
Pro Thr Pro Glu Glu Ala Gln Arg Glu Lys Asp Thr Arg Ile Ser Lys
                995                1000                1005

AAG ATG GAA ACA ATG GGC ATC TAC TTC GCG ACA CCG GAA TGG GTG GCT      2761
Lys Met Glu Thr Met Gly Ile Tyr Phe Ala Thr Pro Glu Trp Val Ala
           1010                1015                1020

CTC AAC GGG CAC CGA GGC CCA AGC CCC GGC CAA CTC AAG TAC TGG CAA      2809
Leu Asn Gly His Arg Gly Pro Ser Pro Gly Gln Leu Lys Tyr Trp Gln
       1025                1030                1035

AAC ACA AGA GAA ATA CCA GAG CCC AAT GAG GAC TAC CCA GAC TAT GTG      2857
Asn Thr Arg Glu Ile Pro Glu Pro Asn Glu Asp Tyr Pro Asp Tyr Val
   1040                1045                1050

CAC GCG GAG AAG AGC CGG TTG GCG TCA GAA GAA CAG ATC CTA CGG GCA      2905
His Ala Glu Lys Ser Arg Leu Ala Ser Glu Glu Gln Ile Leu Arg Ala
1055                1060                1065                1070

GCC ACG TCG ATC TAC GGG GCT CCA GGA CAG GCT GAA CCA CCC CAG GCC      2953
Ala Thr Ser Ile Tyr Gly Ala Pro Gly Gln Ala Glu Pro Pro Gln Ala
               1075                1080                1085
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TTC ATA GAC GAG GTC GCC AGG GTC TAT GAA ATC AAC CAT GGG CGT GGT     3001
Phe Ile Asp Glu Val Ala Arg Val Tyr Glu Ile Asn His Gly Arg Gly
            1090                1095                1100

CCA AAC CAG GAG CAG ATG AAG GAC CTG CTC CTG ACT GCG ATG GAG ATG     3049
Pro Asn Gln Glu Gln Met Lys Asp Leu Leu Leu Thr Ala Met Glu Met
        1105                1110                1115

AAG CAT CGC AAT CCC AGG CGG GCT CCA CCA AAG CCA AAG CCA AAA CCC     3097
Lys His Arg Asn Pro Arg Arg Ala Pro Pro Lys Pro Lys Pro Lys Pro
    1120                1125                1130

AAT GCT CCA TCA CAG AGA CCC CCT GGA CGG CTG GGC CGC TGG ATC AGG     3145
Asn Ala Pro Ser Gln Arg Pro Pro Gly Arg Leu Gly Arg Trp Ile Arg
1135                1140                1145                1150

ACG GTC TCC GAC GAG GAC TTG GAG TGAGGCTCCT GGGAGTCTCC CGACACTACC     3199
Thr Val Ser Asp Glu Asp Leu Glu
                1155

CGCGCAGGTG TGGACACCAA TTCGGCCTTC TACCATCCCA AATTGGATCC GTTCGCGGGT  3259

CCCCT                                                              3264
```

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1013 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

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Met Thr Asn Leu Met Asp His Thr Gln Gln Ile Val Pro Phe Ile Arg
  1               5                  10                  15

Ser Leu Leu Met Pro Thr Thr Gly Pro Ala Ser Ile Pro Asp Asp Thr
            20                  25                  30

Leu Glu Lys His Thr Leu Arg Ser Glu Thr Ser Thr Tyr Asn Leu Thr
        35                  40                  45

Val Gly Asp Thr Gly Ser Gly Leu Ile Val Phe Phe Pro Gly Phe Pro
    50                  55                  60

Gly Ser Val Val Gly Ala His Tyr Thr Leu Gln Ser Ser Gly Asn Tyr
65                  70                  75                  80

Gln Phe Asp Gln Met Leu Leu Thr Ala Gln Asn Leu Pro Ala Ser Tyr
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                85                  90                  95

Asn Tyr Cys Arg Leu Val Ser Arg Ser Leu Thr Val Arg Ser Ser Thr
            100                 105                 110

Leu Pro Gly Gly Val Tyr Ala Leu Asn Gly Thr Ile Asn Ala Val Thr
        115                 120                 125

Phe His Gly Ser Leu Ser Glu Leu Thr Asp Tyr Ser Tyr Asn Gly Leu
    130                 135                 140

Met Ser Ala Thr Ala Asn Ile Asn Asp Lys Ile Gly Asn Val Leu Val
145                 150                 155                 160

Gly Glu Gly Val Thr Val Leu Ser Leu Pro Thr Ser Tyr Asp Leu Ser
                165                 170                 175

Tyr Val Arg Leu Gly Asp Pro Ile Pro Ala Ala Gly Leu Asp Pro Lys
            180                 185                 190

Leu Met Ala Thr Cys Asp Ser Ser Asp Arg Pro Arg Val Tyr Thr Ile
        195                 200                 205

Thr Ala Ala Asp Glu Tyr Gln Phe Ser Ser Gln Leu Ile Pro Ser Gly
    210                 215                 220

Val Lys Thr Thr Leu Phe Ser Ala Asn Ile Asp Ala Leu Thr Ser Phe
225                 230                 235                 240

Ser Val Gly Gly Glu Leu Val Phe Ser Gln Val Thr Ile Gln Ser Ile
                245                 250                 255

Glu Val Asp Val Thr Ile His Phe Ile Gly Phe Asp Gly Thr Asp Val
            260                 265                 270

Ala Val Lys Ala Val Ala Thr Asp Phe Gly Leu Thr Thr Gly Thr Asn
        275                 280                 285

Asn Leu Val Pro Phe Asn Leu Val Val Pro Thr Asn Glu Ile Thr Gln
    290                 295                 300

Pro Ile Thr Ser Met Lys Leu Glu Val Val Thr Tyr Lys Ile Gly Gly
305                 310                 315                 320

Thr Ala Gly Asp Pro Ile Ser Trp Thr Val Ser Gly Thr Leu Ala Val
                325                 330                 335

Thr Val His Gly Gly Asn Tyr Pro Gly Ala Leu Arg Pro Val Thr Leu
            340                 345                 350

Val Ala Tyr Glu Arg Val Ala Ala Gly Ser Val Val Thr Val Ala Gly
        355                 360                 365
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Val Ser Asn Phe Glu Leu Ile Pro Asn Pro Glu Leu Ala Lys Asn Leu
370 375 380

Val Thr Glu Tyr Gly Arg Phe Asp Pro Gly Ala Met Asn Tyr Thr Lys
385 390 395 400

Leu Ile Leu Ser Glu Arg Asp Arg Leu Gly Ile Lys Thr Val Trp Pro
405 410 415

Thr Arg Glu Tyr Thr Asp Phe Arg Glu Tyr Phe Met Glu Val Ala Asp
420 425 430

Leu Asn Ser Pro Leu Lys Ile Ala Gly Ala Phe Gly Phe Lys Asp Ile
435 440 445

Ile Arg Ala Ile Arg Lys Ile Ala Val Pro Val Val Ser Thr Leu Phe
450 455 460

Pro Pro Ala Ala Pro Leu Ala His Ala Ile Gly Glu Gly Val Asp Tyr
465 470 475 480

Leu Leu Gly Asp Glu Ala Gln Ala Ala Ser Gly Thr Ala Arg Ala Ala
485 490 495

Ser Gly Lys Ala Arg Ala Ala Ser Gly Arg Ile Arg Gln Leu Thr Leu
500 505 510

Ala Ala Asp Lys Gly Cys Glu Val Val Ala Asn Met Phe Gln Val Pro
515 520 525

Gln Asn Pro Ile Val Asp Gly Ile Leu Ala Ser Pro Gly Ile Leu Arg
530 535 540

Gly Ala His Asn Leu Asp Cys Val Leu Trp Glu Gly Ala Thr Leu Phe
545 550 555 560

Pro Val Val Ile Thr Thr Leu Glu Asp Glu Leu Thr Pro Lys Ala Leu
565 570 575

Asn Ser Lys Met Phe Ala Val Ile Glu Gly Val Arg Glu Asp Leu Gln
580 585 590

Pro Pro Ser Gln Arg Gly Ser Phe Ile Arg Thr Leu Ser Gly His Arg
595 600 605

Val Tyr Gly Tyr Ala Pro Asp Gly Val Leu Pro Leu Glu Thr Gly Arg
610 615 620

Asp Tyr Thr Val Val Pro Ile Asp Asp Val Trp Asp Asp Ser Ile Met
625 630 635 640

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Leu Ser Gln Asp Pro Ile Pro Pro Ile Ile Gly Asn Ser Gly Asn Leu
                645                 650                 655

Ala Ile Ala Tyr Met Asp Val Phe Arg Pro Lys Val Pro Ile His Val
            660                 665                 670

Ala Met Thr Gly Ala Leu Asn Ala Arg Gly Glu Ile Glu Ser Val Thr
        675                 680                 685

Phe Arg Ser Thr Lys Leu Ala Thr Ala His Arg Leu Gly Met Lys Leu
    690                 695                 700

Ala Gly Pro Gly Ala Tyr Asp Ile Asn Thr Gly Pro Asn Trp Ala Thr
705                 710                 715                 720

Phe Val Lys Arg Phe Pro His Asn Pro Arg Asp Trp Asp Arg Leu Pro
                725                 730                 735

Tyr Leu Asn Leu Pro Tyr Leu Pro Pro Thr Ala Gly Arg Gln Phe His
            740                 745                 750

Leu Ala Leu Ala Ala Ser Glu Phe Lys Glu Thr Pro Glu Leu Glu Asp
        755                 760                 765

Ala Val Arg Ala Met Asp Ala Ala Ala Asn Ala Asp Pro Leu Phe Arg
    770                 775                 780

Ser Ala Leu Gln Val Phe Met Trp Leu Glu Glu Asn Gly Ile Val Thr
785                 790                 795                 800

Asp Met Ala Asn Phe Ala Leu Ser Asp Pro Asn Ala His Arg Met Lys
                805                 810                 815

Asn Phe Leu Ala Asn Ala Pro Gln Ala Gly Ser Lys Ser Gln Arg Ala
            820                 825                 830

Lys Tyr Gly Thr Ala Gly Tyr Gly Val Glu Ala Arg Gly Pro Thr Pro
        835                 840                 845

Glu Glu Ala Gln Arg Glu Lys Asp Thr Arg Ile Ser Lys Lys Met Glu
    850                 855                 860

Thr Met Gly Ile Tyr Phe Ala Thr Pro Glu Trp Val Ala Leu Asn Gly
865                 870                 875                 880

His Arg Gly Pro Ser Pro Gly Gln Leu Lys Tyr Trp Gln Asn Thr Arg
                885                 890                 895

Glu Ile Pro Glu Pro Asn Glu Asp Tyr Pro Asp Tyr Val His Ala Glu
            900                 905                 910
```

Lys Ser Arg Leu Ala Ser Glu Glu Gln Ile Leu Arg Ala Ala Thr Ser
915 920 925

Ile Tyr Gly Ala Pro Gly Gln Ala Glu Pro Pro Gln Ala Phe Ile Asp
930 935 940

Glu Val Ala Arg Val Tyr Glu Ile Asn His Gly Arg Gly Pro Asn Gln
945 950 955 960

Glu Gln Met Lys Asp Leu Leu Leu Thr Ala Met Glu Met Lys His Arg
965 970 975

Asn Pro Arg Arg Ala Pro Pro Lys Pro Lys Pro Lys Pro Asn Ala Pro
980 985 990

Ser Gln Arg Pro Pro Gly Arg Leu Gly Arg Trp Ile Arg Thr Val Ser
995 1000 1005

Asp Glu Asp Leu Glu
1010

Claims

1. A method for preparing live Birnavirus, comprising the following steps:

preparing a cDNA containing infectious bursal disease virus genome segments A and B,

transcribing said cDNA to produce synthetic RNA transcripts,

transfecting host cells with said synthetic RNA transcripts,

incubating said host cells in a culture medium, and

isolating live infectious bursal disease virus from said culture medium.

2. The method according to claim 1, wherein said Birnavirus is infectious bursal disease virus.

3. The method according to claim 1, wherein said host cells are African green monkey Vero cells.

4. The method according to claim 1, wherein said segments A and B of said cDNA are independently prepared.

5. The method according to claim 4, wherein said segment A is present in plasmid pUC19FLAD78 or pUC18FLA23.

6. The method according to claim 4, wherein said segment B is present in plasmid pUC18FLBP2.

7. A live infectious bursal disease virus, wherein said virus is made by a process comprising the steps of preparing a cDNA containing infectious bursal disease virus genome segments A and B,

transcribing said cDNA to produce a synthetic RNA transcript,

transfecting a host cell with said synthetic RNA transcript,

incubating said host cell in a culture medium, and

isolating live infectious bursal disease virus from said culture medium.

8. A synthetic RNA encoding proteins VP1, VP2, VP3, VP4, and VP5 of infectious bursal disease virus.

9. A host cell transfected with the synthetic RNA according to claim 8.

10. A cDNA containing at least a portion of the infectious bursal disease virus genome selected from the group consisting of segment A,

segment B and segments A and B of infectious bursal disease virus, wherein said cDNA includes the 5' and 3' terminii of said segments.

11. A recombinant vector comprising the cDNA according to claim 10.

12. The vector according to claim 11, wherein said vector is a plasmid.

13. The vector according to claim 12, wherein said plasmid is selected from the group consisting of pUC19FLAD78, pUC18FLA23 and pUC19FLBP2.

14. A host cell transformed with the vector according to claim 11.

15. A vaccine comprising an infectious bursal disease virus according to claim 7, wherein said infectious bursal disease virus is inactivated or attenuated prior to administration.

16. A method for producing a live infectious bursal disease virus vaccine, comprising the steps of

preparing a full-length cDNA containing infectious bursal disease virus genome segments A and B,

transcribing said cDNA to produce synthetic RNA transcripts,

purifying said synthetic RNA transcripts,

transfecting host cells with said purified RNA transcripts,

incubating said host cells in a culture medium,

isolating live infectious bursal disease virus from said culture medium,

attenuating said live infectious bursal disease virus to produce a virus with reduced virulence, and

combining said live infectious bursal disease virus with a pharmaceutically acceptable carrier to produce a live infectious bursal disease virus vaccine.

17. The method according to claim 16, wherein said live infectious bursal disease virus is attenuated by serial passage or site directed mutagenesis.

18. The method according to claim 1, wherein said host cells are poultry cells.

19. The method according to claim 18, wherein said poultry cells are chicken, turkey, or quail cells.

20. The method according to claim 19, wherein said poultry cells are chicken embryo fibroblast cells or chicken embryo kidney cells.

Fig. 1

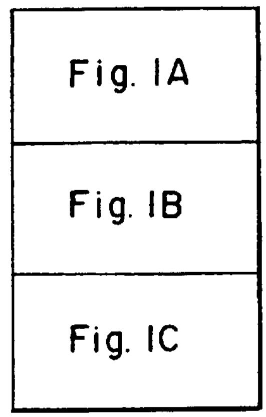


Fig. 4

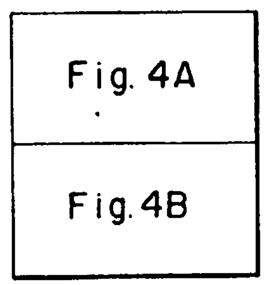


Fig. 5

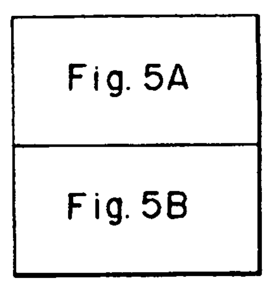
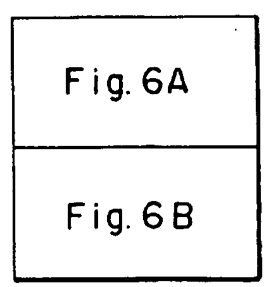


Fig. 6



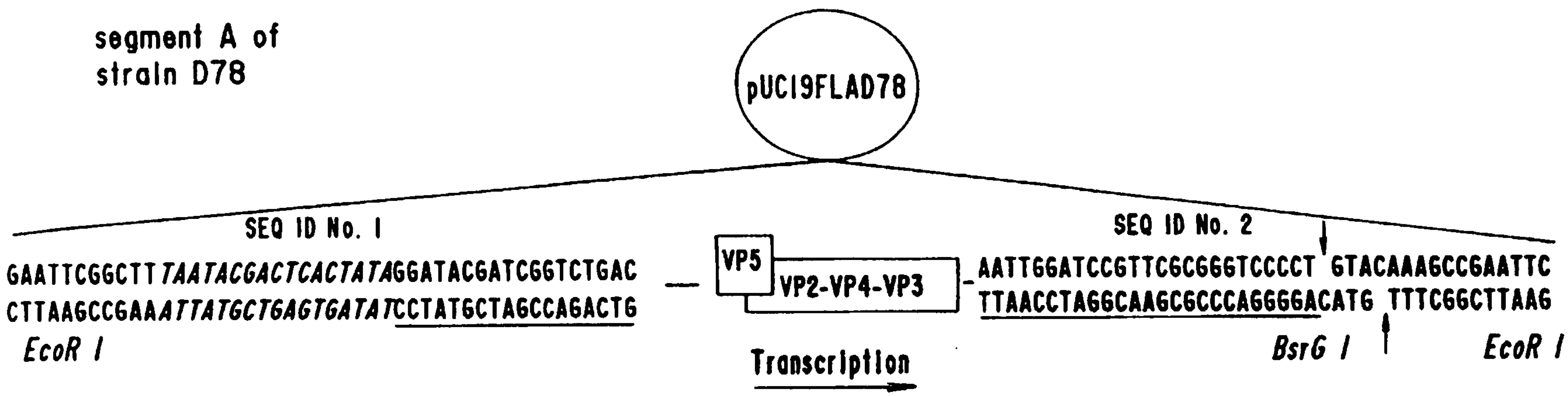

segment A of strain D78
pUC19FLAD78
SEQ ID No. 1
GAATTCGGCTTTAATACGACTCACTATAGGATACGATCGGTCTGAC
CTTAAGCCGAAATTATGCTGAGTGATATCCTATGCTAGCCAGACTG
EcoR I
VP5
VP2-VP4-VP3
Transcription
SEQ ID No. 2
AATTGGATCCGTTCGCGGGTCCCCT GTACAAAGCCGAATTC
TTAACCTAGGCAAGCGCCCAGGGGACATG TTTCGGCTTAAG
BsrG I
EcoR I

Fig.1A

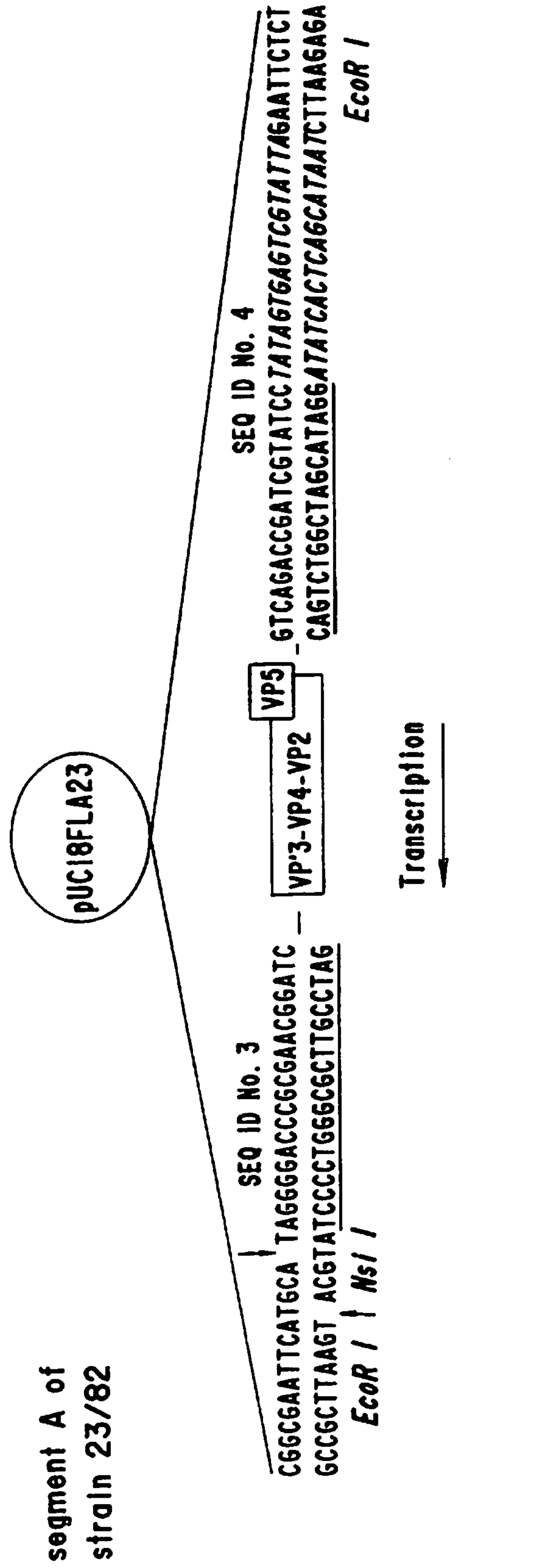

segment A of
strain 23/82
SEQ ID No. 3
CGGCGAATTCATGCA TAGGGGACCCGCGAACGGATC
GCCGCTTAAGT ACGTATCCCCTGGGCGCTTGCCTAG
EcoR I
Nsi I
pUC18FLA23
VP'3-VP4-VP2
VP5
Transcription
SEQ ID No. 4
GTCAGACCGATCGTATCCTATAGTGAGTCGTATTAGAATTCTCT
CAGTCTGGCTAGCATAGGATATCACTCAGCATAATCTTAAGAGA
EcoR I

Fig.1B

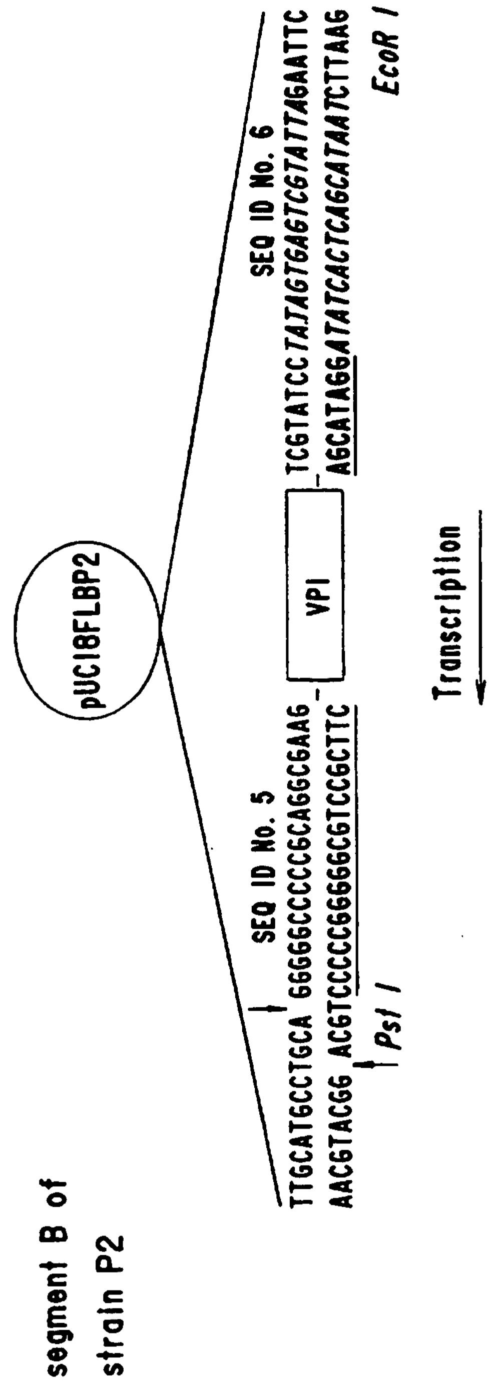

segment B of
strain P2
pUC18FLBP2
SEQ ID No. 5
TTGCATGCCTGCA GGGGGCCCCGCAGGCGAAG
AACGTACGG ACGTCCCCCGGGGCGTCCGCTTC
Pst I
VP1
SEQ ID No. 6
TCGTATCCTATAGTGAGTCGTATTAGAATTC
AGCATAGGATATCACTCAGCATAATCTTAAG
EcoR I
Transcription

Fig.1C

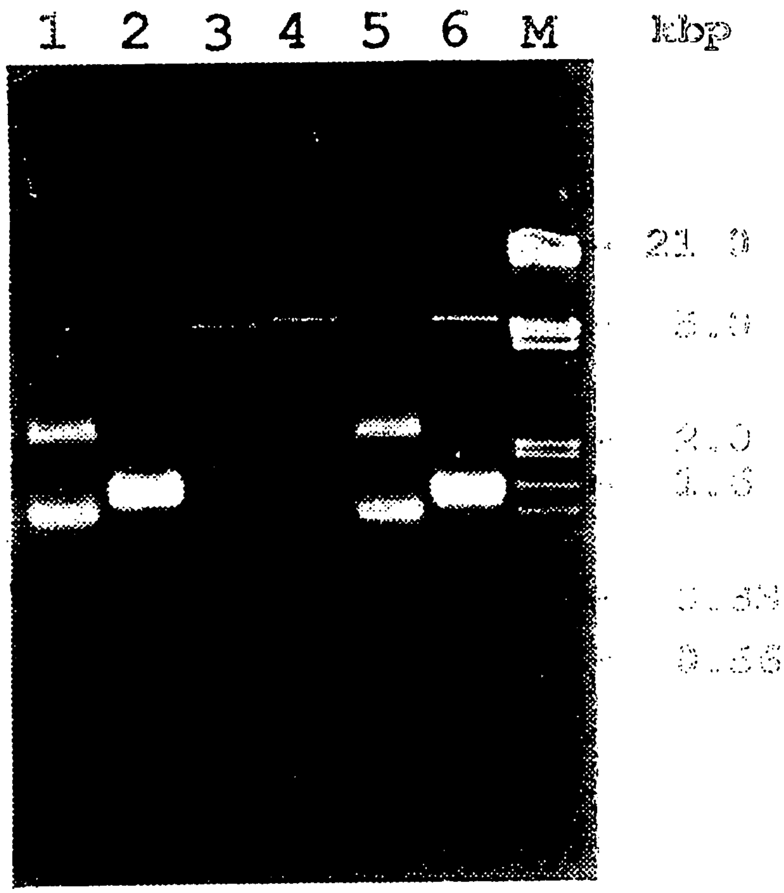


Fig. 2

Segment A

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                 530       540       550       560       570       580
23-82A       GGAAGCCTGAGTGAGTTGACTGACTACAGCTACAACGGGCTGATGTCAGCCACTGCGAAC
SEQ ID No. 7
23A/P2B      GGAAGCCTGAGTGAGTTGACTGACTACAGCTACAACGGGCTGATGTCAGCCACTGCGAAC
SEQ ID No. 8
P2A          GGAAGCCTGAGTGAACTGACAGATGTTAGCTACAATGGGTTGATGTCTGCAACAGCCAAC
SEQ ID No. 9     530       540       550       560       570       580

                 590       600       610       620       630       640
23-82A       ATCAACGACAAGATCGGGAACGTTCTAGTTGGAGAAGGGGTGACTGTTCTCAGTCTACCG
SEQ ID No. 7
23A/P2B      ATCAACGACAAGATCGGGAACGTTCTAGTTGGAGAAGGGGTGACTGTTCTCAGTCTACCG
SEQ ID No. 8
P2A          ATCAACGACAAAATTGGGAACGTCCTAGTAGGGGAAGGGGTCACCGTCCTCAGCTTACCC
SEQ ID No. 9     590       600       610       620       630       640
```

Fig.3A

Segment B

```
                        130       140       150       160       170       180
23-82B             TTTTCAATAGTCCACAGGCGCGAACGAAGATCTCAGCAGCGTTCGGCATAAAGCCTACTG
SEQ ID No. 10
23A/P2B            TTTTCAACAGTCCACAGGCGCGAAGCACGATCTCAGCAGCGTTCGGCATAAAGCCTACTG
SEQ ID No. 11
P2B                TTTTCAACAGTCCACAGGCGCGAAGCACGATCTCAGCAGCGTTCGGCATAAAGCCTACTG
SEQ ID No. 12           130       140       150       160       170       180

                        190       200       210       220       230       240
23-82B             CTGGACAAGACGTGGAAGAACTCTTGATCCCCAAAGTCTGGGTGCCACCTGAGGATCCGC
SEQ ID No. 10
23A/P2B            CTGGACAAGACGTGGAAGAACTCTTGATCCCTAAAGTTTGGGTGCCACCTGAGGATCCGC
SEQ ID No. 11
P2B                CTGGACAAGACGTGGAAGAACTCTTGATCCCTAAAGTTTGGGTGCCACCTGAGGATCCGC
SEQ ID No. 12           190       200       210       220       230       240
```

Fig.3B

Fig.4A

```
              10        20        30        40        50        60        70
               |         |         |         |         |         |         |
   1 GGATACGATCGGTCTGACCCCGGGGGAGTCACCCGGGGACAGGCCATCACTGCCTTGTTCCTGGTTGGAA
  71 CTCCTCTTTCTGCTGTACTATCGTTGATGGTGAGTAGAGATCAGACAAACGATCGCAGCGATGACAAACC
 141 TGATGGATCACACCCAACAGATTGTTCCGTTCATACGGAGCCTTCTGATGCCAACGACCGGACCGGCGTC
 211 CATTCCGGACGACACCCTGGAGAAGCACACACTCAGGTCCGAAACCTCGACTTACAACTTGACTGTAGGG
 281 GATACAGGGTCAGGACTAATTGTCTTTTTCCCTGGATTCCCTGGTTCAGTTGTAGGTGCTCACTACACAC
 351 TGCAGAGCAGTGGGAACTACCAATTCGACCAGATGCTCCTGACAGCGCAGAACCTGCCTGCCAGCTACAA
 421 CTACTGCAGGCTAGTGAGCAGGAGTCTAACCGTACGGTCAAGCACACTCCCTGGTGGCGTTTATGCACTA
 491 AACGGAACCATAAACGCAGTGACCTTCCACGGAAGCCTGAGTGAGTTGACTGACTACAGCTACAACGGGC
 561 TGATGTCAGCCACTGCGAACATCAACGACAAGATCGGGAACGTTCTAGTTGGAGAAGGGGTGACTGTTCT
 631 CAGTCTACCGACTTCATATGACCTTAGTTATGTGAGACTCGGTGACCCCATCCCCGCAGCAGGACTCGAC
 701 CCGAAGTTGATGGCCACGTGCGACAGTAGTGACAGACCCAGAGTCTACACCATAACAGCTGCAGATGAAT
 771 ACCAATTCTCGTCACAACTCATCCCGAGTGGCGTGAAGACCACACTGTTCTCCGCCAACATCGATGCTCT
 841 CACCAGCTTCAGCGTTGGTGGTGAGCTTGTCTTCAGCCAAGTAACGATCCAAAGCATTGAAGTGGACGTC
 911 ACCATTCACTTCATTGGGTTTGACGGGACAGACGTAGCAGTCAAGGCAGTTGCAACAGACTTTGGGCTGA
 981 CAACTGGGACAAACAACCTTGTGCCATTCAACCTGGTGGTCCCAACAAATGAGATCACCCAGCCCATCAC
1051 TTCCATGAAACTAGAGGTTGTGACCTACAAGATTGGCGGCACCGCTGGTGACCCAATATCATGGACAGTG
1121 AGTGGTACACTAGCTGTGACGGTGCACGGAGGCAACTACCCTGGGGCTCTCCGTCCTGTCACCCTGGTGG
1191 CCTATGAACGAGTGGCTGCAGGATCTGTTGTCACAGTTGCAGGGGTGAGCAACTTCGAGCTAATCCCCAA
1261 CCCTGAGCTTGCAAAGAACCTAGTTACAGAGTATGGCCGCTTTGACCCCGGAGCAATGAACTACACCAAA
1331 CTAATACTGAGTGAGAGAGATCGTCTAGGCATCAAGACAGTCTGGCCCACCAGGGAGTACACCGATTTGA
1401 GGGAGTACTTCATGGAGGTTGCAGATCTCAACTCACCCCTAAAGATTGCAGGAGCATTTGGCTTTAAGGA
1471 CATAATCCGAGCCATTCGGAAGATTGCGGTGCCAGTGGTATCCACACTCTTCCCTCCAGCTGCACCCCTA
1541 GCACATGCAATCGGAGAAGGTGTAGACTACCTCCTGGGCGACGAGGCCCAAGCAGCCTCAGGGACAGCTC
1611 GAGCCGCGTCAGGAAAAGCTAGAGCTGCCTCAGGACGAATAAGGCAGCTAACTCTCGCAGCTGACAAGGG
1681 GTGCGAGGTAGTCGCCAACATGTTCCAGGTGCCCCAGAATCCCATTGTTGATGGCATTCTGGCATCCCCA
1751 GGAATCCTGCGTGGCGCACACAACCTCGACTGCGTGCTATGGAGGGAGCCACTCTTTTCCCTGTTGTCA
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1821  TTACGACACTCGAGGATGAGCTGACCCCCAAGGCACTGAACAGCAAAATGTTTGCTGTCATTGAAGGTGT
1891  GCGAGAGGACCTCCAGCCTCCATCCCAACGGGGATCCTTCATTCGAACTCTCTCTGGCCATAGAGTCTAT
1961  GGCTATGCCCCAGACGGAGTACTGCCTCTGGAGACCGGGAGAGACTACACCGTTGTCCCAATTGATGATG
2031  TGTGGGACGATAGCATAATGCTGTCGCAGGACCCCATACCTCCAATCATAGGGAACAGCGGCAACCTAGC
2101  CATAGCATACATGGATGTCTTCAGGCCCAAGGTCCCCATCCACGTGGCTATGACAGGGGCCCTCAATGCC
2171  CGCGGTGAGATCGAGAGTGTTACGTTCCGVAGCACCAAACTCGCCACAGCCCACCGACTTGGCATGAAGT
2241  TAGCTGGTCCTGGAGCCTATGACATTAATACAGGACCTAACTGGGCAACGTTCGTCAAACGTTTCCCTCA
2311  CAATCCCCGAGACTGGGACAGGTTGCCCTACCTCAACCTTCCTTATCTCCCACCAACAGCAGGACGTCAG
2381  TTCCATCTAGCCCTGGCTGCCTCCGAGTTCAAAGAGACCCCAGAACTCGAAGACGCTGTGCGCGCAATGG
2451  ATGCCGCTGCAAATGCCGACCCATTGTTCCGCTCAGCTCTCCAGGTCTTCATGTGGTTGGAAGAAAACGG
2521  GATTGTGACCGACATGGCTAACTTCGCCCTCAGCGACCCAAACGCGCATAGGATGAAAAACTTCCTAGCA
2591  AACGCACCCCAGGCTGGAAGCAAGTCGCAGAGGGCCAAGTATGGCACGGCAGGCTACGGAGTGGAGGCTC
2661  GAGGCCCCACACCAGAAGAGGCACAGAGGGAAAAAGACACACGGATCTCCAAGAAGATGGAAACAATGGG
2731  CATCTACTTCGCGACACCGGAATGGGTGGCTCTCAACGGGCACCGAGGCCCAAGCCCCGGCCAACTCAAG
2801  TACTGGCAAAACACAAGAGAAATACCAGAGCCCAATGAGGACTACCCAGACTATGTGCACGCGGAGAAGA
2871  GCCGGTTGGCGTCAGAAGAACAGATCCTACGGGCAGCCACGTCGATCTACGGGGCTCCAGGACAGGCTGA
2941  ACCACCCCAGGCCTTCATAGACGAGGTCGCCAGGGTCTATGAAATCAACCATGGGCGTGGTCCAAACCAG
3011  GAGCAGATGAAGGACCTGCTCCTGACTGCGATGGAGATGAAGCATCGCAATCCCAGGCGGGCTCCACCAA
3081  AGCCAAAGCCAAAACCCAATGCTCCATCACAGAGACCCCCTGGACGGCTGGGCCGCTGGATCAGGACGGT
3151  CTCCGACGAGGACTTGGAGTGAGGCTCCTGGGAGTCTCCCGACACTACCCGCGCAGGTGTGGACACCAAT
3221  TCGGCCTTCTACCATCCCAAATTGGATCCGTTCGCGGGTCCCCT
```

Total number of bases is: 3264.
DNA sequence composition: 834 A; 942 C; 853 G; 635 T;

Sequence name: 23-82A (SEQ ID NOS: 31 and 33)

Fig.4B

Fig.5A

```
        10        20        30        40        50        60        70
        |         |         |         |         |         |         |
1    GGATACGATCGGTCTGACCCCGGGGGAGTCACCCGGGGACAGGCCGTCAAGGCCTTGTTCCAGGATGGGA
71   CTCCTCCTTCTACAACGCTATCATTGATGGTTAGTAGAGATCAGACAAACGATCGCAGCGATGACAAACC
141  TGCAAGATCAAACCCAACAGATTGTTCCGTTCATACGGAGCCTTCTGATGCCAACAACCGGACCGGCGTC
211  CATTCCGGACGACACCCTGGAGAAGCACACTCTCAGGTCAGAGACCTCGACCTACAATTTGACTGTGGGG
281  GACACAGGGTCAGGGCTAATTGTCTTTTTCCCTGGATTCCCTGGCTCAATTGTGGGTGCTCACTACACAC
351  TGCAGGGCAATGGGAACTACAAGTTCGATCAGATGCTCCTGACTGCCCAGAACCTACCGGCCAGTTACAA
421  CTACTGCAGGCTAGTGAGTCGGAGTCTCACAGTGAGGTCAAGCACACTTCCTGGTGGCGTTTATGCACTA
491  AACGGCACCATAAACGCCGTGACCTTCCAAGGAAGCCTGAGTGAACTGACAGATGTTAGCTACAATGGGT
561  TGATGTCTGCAACAGCCAACATCAACGACAAAATTGGGAACGTCCTAGTAGGGGAAGGGGTCACCGTCCT
631  CAGCTTACCCACATCATATGATCTTGGGTATGTGAGGCTTGGTGACCCCATTCCCGCAATAGGGCTTGAC
701  CCAAAAATGGTAGCCACATGTGACAGCAGTGACAGGCCCAGAGTCTACACCATAACTGCAGCCGATGATT
771  ACCAATTCTCATCACAGTACCAACCAGGTGGGGTAACAATCACACTGTTCTCAGCCAACATTGATGCCAT
841  CACAAGCCTCAGCGTTGGGGGAGAGCTCGTGTTTCAAACAAGCGTCCACGGCCTTGTACTGGGCGCCACC
911  ATCTACCTCATAGGCTTTGATGGGACAACGGTAATCACCAGGGCTGTGGCCGCAAACAATGGGCTGACGA
981  CCGGCACCGACAACCTTATGCCATTCAATCTTGTGATTCCAACAAACGAGATAACCCAGCCAATCACATC
1051 CATCAAACTGGAGATAGTGACCTCCAAAAGTGGTGGTCAGGCAGGGGATCAGATGTCATGGTCGGCAAGA
1121 GGGAGCCTAGCAGTGACGATCCATGGTGGCAACTATCCAGGGGCCCTCCGTCCCGTCACGCTAGTGGCCT
1191 ACGAAAGAGTGGCAACAGGATCCGTCGTTACGGTCGCTGGGGTGAGCAACTTCGAGCTGATCCCAAATCC
1261 TGAACTAGCAAAGAACCTGGTTACAGAATACGGCCGATTTGACCCAGGAGCCATGAACTACACAAAATTG
1331 ATACTGAGTGAGAGGGACCGTCTTGGCATCAAGACCGTCTGGCCAACAAGGGAGTACACTGACTTTCGTG
1401 AATACTTCATGGAGGTGGCCGACCTCAACTCTCCCCTGAAGATTGCAGGAGCATTCGGCTTCAAAGACAT
1471 AATCCGGGCCATAAGGAGGATAGCTGTGCCGGTGGTCTCCACATTGTTCCCACCTGCCGCTCCCCTAGCC
1541 CATGCAATTGGGGAAGGTGTAGACTACCTGCTGGGCGATGAGGCACAGGCTGCTTCAGGAACTGCTCGAG
1611 CCGCGTCAGGAAAAGCAAGAGCTGCCTCAGGCCGCATAAGGCAGCTGACTCTCGCCGCCGACAAGGGGTA
1681 CGAGGTAGTCGCGAATCTATTCCAGGTGCCCCAGAATCCCGTAGTCGACGGGATTCTTGCTTCACCTGGG
1751 GTACTCCGCGGTGCACACAACCTCGACTGCGTGTTAAGAGAGGGTGCCACGCTATTCCCTGTGGTTATTA
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1821  CGACAGTGGAAGACGCCATGACACCCAAAGCATTGAACAGCAAAATGTTTGCTGTCATTGAAGGCGTGCG
1891  AGAAGACCTCCAACCTCCATCTCAAAGAGGATCCTTCATACGAACTCTCTCTGGACACAGAGTCTATGGA
1961  TATGCTCCAGATGGGGTACTTCCACTGGAGACTGGGAGAGACTACACCGTTGTCCCAATAGATGATGTCT
2031  GGGACGACAGCATTATGCTGTCCAAAGATCCCATACCTCCTATTGTGGGAAACAGTGGAAATCTAGCCAT
2101  AGCTTACATGGATGTGTTTCGACCCAAAGTCCCAATCCATGTGGCTATGACGGGAGCCCTCAATGCTTGT
2171  GGCGAGATTGAGAAAGTAAGCTTTAGAAGCACCAAGCTCGCCACTGCACACCGACTTGGCCTTAGGTTGG
2241  CTGGTCCCGGAGCATTCGATGTAAACACCGGGCCCAACTGGGCAACGTTCATCAAACGTTTCCCTCACAA
2311  TCCACGCCACTGGGACAGGCTCCCCTACCTCAACCTACCATACCTTCCACCCAATGCAGGACGCCAGTAC
2381  CACCTTGCCATGGCTGCATCAGAGTTCAAAGAGACCCCCGAACTCGAGAGTGCCGTCAGAGCAATGGAAG
2451  CAGCAGCCAACGTGGACCCACTATTCCAATCTGCACTCAGTGTGTTCATGTGGCTGGAAGAGAATGGGAT
2521  TGTGACTGACATGGCCAACTTCGCACTCAGCGACCCGAACGCCCATCGGATGCGAAATTTTCTTGCAAAC
2591  GCACCACAAGCAGGCAGCAAGTCGCAAAGGGCCAAGTACGGGACAGCAGGCTACGGAGTGGAGGCTCGGG
2661  GCCCCACACCAGAGGAAGCACAGAGGGAAAAAGACACACGGATCTCAAAGAAGATGGAGACCATGGGCAT
2731  CTACTTTGCAACACCAGAATGGGTAGCACTCAATGGCACCGAGGGCCAAGCCCCGGCCAGCTAAAGTAC
2801  TGGCAGAACACACGAGAAATACCGGACCCAAACGAGGACTATCTAGACTACGTGCATGCAGAGAAGAGCC
2871  GGTTGGCATCAGAAGAACAAATCCTAAGGGCAGCTACGTCGATCTACGGGGCTCCAGGACAGGCAGAGCC
2941  ACCCCAAGCTTTCATAGACGAAGTTGCCAAAGTCTATGAAATCAACCATGGACGTGGCCCAAACCAAGAA
3011  CAGATGAAAGATCTGCTCTTGACTGCGATGGAGATGAAGCATCGCAATCCCAGGCGGGCTCTACCAAAGC
3081  CCAAGCCAAAACCCAATGCTCCAACACAGAGACCCCCTGGTCGGCTGGGCCGCTGGATCAGGACCGTCTC
3151  TGATGAGGACCTTGAGTGAGGCTCCTGGGAGTCTCCCGACACCACCCGCGCAGGTGTGGACACCAATTCG
3221  GCCTTACAACATCCCAAATTGGATCCGTTCGCGGGTCCCCT
```

Total number of bases is: 3261.

DNA sequence composition: 873 A; 909 C; 847 G; 632 T; 0 OTHER;

Sequence name: D78F (SEQ ID NOS: 27 and 29)

Fig.5B

Fig.6A

	10 20 30 40 50 60 70
1	GGATACGATGGGTCTGACCCTCTGGGAGTCACGAATTAACGTGGCTACTAGGGGCGATACCCGCCGCTGG
71	CCGCCACGTTAGTGGCTCCTCTTCTTGATGATTCTGCCACCATGAGTGACATTTTCAACAGTCCACAGGC
141	GCGAAGCACGATCTCAGCAGCGTTCGGCATAAAGCCTACTGCTGGACAAGACGTGGAAGAACTCTTGATC
211	CCTAAAGTTTGGGTGCCACCTGAGGATCCGCTTGCCAGCCCTAGTCGACTGGCAAAGTTCCTCAGAGAGA
281	ACGGCTACAAAGTTTTGCAGCCACGGTCTCTGCCCGAGAATGAGGAGTATGAGACCGACCAAATACTCCC
351	AGACTTAGCATGGATGCGACAGATAGAAGGGGCTGTTTTAAAACCCACTCTATCTCTCCCTATTGGAGAT
421	CAGGAGTACTTCCCAAAGTACTACCCAACACATCGCCCTAGCAAGGAGAAGCCCAATGCGTACCCGCCAG
491	ACATCGCACTACTCAAGCAGATGATTTACCTGTTTCTCCAGGTTCCAGAGGCCAACGAGGGCCTAAAGGA
561	TGAAGTAACCCTCTTGACCCAAAACATAAGGGACAAGGCCTATGGAAGTGGGACCTACATGGGACAAGCA
631	AATCGACTTGTGGCCATGAAGGAGGTCGCCACTGGAAGAAACCCAAACAAGGATCCTCTAAAGCTTGGGT
701	ACACTTTTGAGAGCATCGCGCAGCTACTTGACATCACACTACCGGTAGGCCCACCCGGTGAGGATGACAA
771	GCCCTGGGTGCCACTCACAAGAGTGCCGTCACGGATGTTGGTGCTGACGGGAGACGTAGATGGCGACTTT
841	GAGGTTGAAGATTACCTTCCCAAAATCAACCTCAAGTCATCAAGTGGACTACCATATGTAGGTCGCACCA
911	AAGGAGAGACAATTGGCGAGATGATAGCTATCTCAAACCAGTTTCTCAGAGAGCTATCAACACTGTTGAA
981	GCAAGGTGCAGGGACAAAGGGGTCAAACAAGAAGAAGCTACTCAGCATGTTAAGTGACTATTGGTACTTA
1051	TCATGCGGGCTTTTGTTTCCAAAGGCTGAAAGGTACGACAAAAGTACATGGCTCACCAAGACCCGGAACA
1121	TATGGTCAGCTCCATCCCCAACACACCTCATGATCTCTATGATCACCTGGCCCGTGATGTCCAACAGCCC
1191	AAATAACGTGTTGAACATTGAAGGGTGTCCATCACTCTACAAATTCAACCCGTTCAGAGGAGGGTTGAAC
1261	AGGATCGTCGAGTGGATATTGGCCCCGGAAGAACCCAAGGCTCTTGTATATGCGGACAACATATACATTG
1331	TCCACTCAAACACGTGGTACTCAATTGACCTAGAGAAGGGTGAGGCAAACTGCACTCGCCAACACATGCA
1401	AGCCGCAATGTACTACATACTCACCAGAGGGTGGTCAGACAACGGCGACCCAATGTTCAATCAAACATGG
1471	GCCACCTTTGCCATGAACATTGCCCCTGCTCTAGTGGTGGACTCATCGTGCCTGATAATGAACCTGCAAA
1541	TTAAGACCTATGGTCAAGGCAGCGGGAATGCAGCCACGTTCATCAACAACCACCTCTTGAGCACACTAGT
1611	GCTTGACCAGTGGAACCTGATGAGACAGCCCAGACCAGACAGCGAGGAGTTCAAATCAATTGAGGACAAG
1681	CTAGGTATCAACTTTAAGATTGAGAGGTCCATTGATGATATCAGGGGCAAGCTGAGACAGCTTGTCCTCC
1751	TTGCACAACCAGGGTACCTGAGTGGGGGGGTTGAACCAGAACAATCCAGCCCAACTGTTGAGCTTGACCT

1821 ACTAGGGTGGTCAGCTACATACAGCAAAGATCTCGGGATCTATGTGCCGGTGCTTGACAAGGAACGCCTA
1891 TTTTGTTCTGCTGCGTATCCCAAGGGAGTAGAGAACAAGAGTCTCAAGTCCAAAGTCGGGATCGAGCAGG
1961 CATACAAGGTAGTCAGGTATGAGGCGTTGAGGTTGGTAGGTGGTTGGAACTACCCACTCCTGAACAAAGC
2031 CTGCAAGAATAACGCAGGCGCCGCTCGGCGGCATCTGGAGGCCAAGGGGTTCCCACTCGACGAGTTCCTA
2101 GCCGAGTGGTCTGAGCTGTCAGAGTTCGGTGAGGCCTTCGAAGGCTTCAATATCAAGCTGACCGTAACAT
2171 CTGAGAGCCTAGCCGAACTGAACAAGCCAGTACCCCCCAAGCCCCCAAATGTCAACAGACCAGTCAACAC
2241 TGGGGGACTCAAGGCAGTCAGCAACGCCCTCAAGACCGGTCGGTACAGGAACGAAGCCGGACTGAGTGGT
2311 CTCGTCCTTCTAGCCACAGCAAGAAGCCGTCTGCAAGATGCAGTTAAGGCCAAGGCAGAAGCCGAGAAAC
2381 TCCACAAGTCCAAGCCAGACGACCCCGATGCAGACTGGTTCGAAAGATCAGAAACTCTGTCAGACCTTCT
2451 GGAGAAAGCCGACATCGCCAGCAAGGTCGCCCACTCAGCACTCGTGGAAACAAGCGACGCCCTTGAAGCA
2521 GTTCAGTCGACTTCCGTGTACACCCCCAAGTACCCAGAAGTCAAGAACCCACAGACCGCCTCCAACCCCG
2591 TTGTTGGGCTCCACCTGCCCGCCAAGAGAGCCACCGGTGTCCAGGCCGCTCTTCTCGGAGCAGGAACGAG
2661 CAGACCAATGGGGATGGAGGCCCCAACACGGTCCAAGAACGCCGTGAAAATGGCCAAACGGCGGCAACGC
2731 CAAAAGGAGAGCCGCTAACAGCCATGATGGGAACCACTCAAGAAGAGGACACTAATCCCAGACCCCGTAT
2801 CCCCGGCCTTCGCCTGCGGGGGCCCCC

Total number of bases is: 2827.

DNA sequence composition: 796 A; 770 C; 724 G; 537 T; 0 OTHER;

Sequence name: P2B (SEQ ID No: 25)

Fig.6B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/12955

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/184.1, 204.1, 816, 826; 435/71.1, 235.1, 236, 237, 238, 239, 320.1; 536/23.72

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, STN-MEDLINE, BIOSIS, CAPLUS, CABA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MUNDT et al. Complete Nucleotide Sequences of 5'- and 3' Noncoding Regions of Both Genome Segments of Different Strains of Infectious Bursal Disease Virus. Virology. 1995, Vol. 209, pages 10-18, see entire document.	1-2, 4-20
X	US 4,530,831 A (LUTTICKEN ET AL) 23 JULY 1985 (07/23/85), see entire document.	7, 15-20
X	US 5,192,539 A (VAN DER MAREL ET AL) 09 MARCH 1993 (09/03/93), see entire document.	1-3, 7, 15-20
X	MUNDT et al. Identification of a novel viral protein in infectious bursal disease virus-infected cells. Journal of General Virology. 1995, Vol. 76, pages 437-443, see entire document.	8

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 SEPTEMBER 1997	10 NOV 1997

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	DATQUAN LEE
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BAYLISS et al. A comparison of the sequences of segment A of four infectious bursal disease virus strain and identification of a variable region in VP2. Journal of General Virology. 1990, Vol. 71, pages 1303-1312, see entire document.	1-2, 5-8, 10-13
Y	MORGAN et al. Sequence of the Small Double-Stranded RNA Genomic Segment of Infectious Bursal Disease Virus and Its Deduced 90kDa Product. Virology. 1988, Vol. 163, pages 240-242, see entire document.	1-20
Y	SPIES et al. Nucleotide sequence of infectious bursal disease virus genome segment A delineates two major open reading frames. Nucleic Acids Research. 1989, Vol. 17, No. 19, page 7982, see entire document.	1-20
Y	WO 91/16925 A1 (UNIVERSITY OF MARYLAND at COLLEGE PARK) 14 NOVEMBER 1991 (14/11/91), see entire document.	1-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/12955

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 39/00, 39/38, 39/12; C12P 21/04; C12N 7/00, 7/01, 7/02, 7/04, 7/06, 7/08, 15/00, 15/09, 15/63, 15/70, 15/74

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

424/184.1, 204.1, 816, 826; 435/71.1, 235.1, 236, 237, 238, 239, 320.1; 536/23.72